The Chemistry of Compounds Containing Conjugated Seven-membered Ring Systems, with Special Reference to Azulenes.

by

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PREFACE

This thesis is the result of research training carried out in the Chemistry Department of the University of Edinburgh from September 1953, and was made possible by the assistance of a Maintenance Grant from the Department of Scientific and Industrial Research. The writer wishes to express her thanks to Professor E.L. Hirst and Dr. W.H. Stafford for their guidance and inspiration during this initiation into chemical research. She also wishes to thank Dr. G. McLennan for molecular weight determinations and assistance with X-ray powder photography, Dr. Whitely and Dr. Flett of I.C.I. Billingham and Blackley respectively for determinations of infra red spectra and Mr. A. Voigt for certain of the absorption curves shown in figs.1 and 12.

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CONTENTS

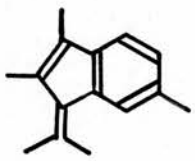
HISTORICAL DEVELOPMENT OF AZULENE CHEMISTRY.

Only the material directly connected with the elucidation of the carbon skeleton or the electronic system, e.g. spectra and reactivity, is given.

Certain essential oils are blue while others become blue on heating to high temperature or on treatment with acid. To the blue material the generic name "azulene" was given by Piesse in 1863 (Chem. News, 1863, 8, 245). Semmler in Aetherische Oele, Vol.III, p.260, Viet and Co., Liepzig, 1906, considered it striking that a molecule of such low boiling point should be so highly coloured. He suggested that azulene consists of two sesquiterpene residues, combined in the manner of indigo, which dissociate to colourless fragments in the gas phase and recombine on liquefying. This belief persisted in the literature until it was shown by Pfau and Plattner (Helv. Chim. Acta, 1936, 19, 858) that azulene is a monomer.

Sherndal (J.A.C.S., 1915, 37, 167, 1537) observed that the blue material in these oils formed an addition compound with mineral acids, and was regenerated on dilution making its isolation possible. Using cubeb oil, he found that the material had an empirical formula of $C_{15}H_{18}$ and that on hydrogenation over palladium it added eight atoms of hydrogen. He regarded this

product as a saturated tricyclic compound of the dihydro-sesquiterpene type, and azulene as an aromatic tricyclic compound containing a benzene ring and a double bond. Misleading evidence was provided by Kremers (J.A.C.S., 1923, 45, 717) who described the products of permanganate oxidation of the azulene from oil of milfoil as acetone and a methylated phthalic acid and he gave it the formula I.



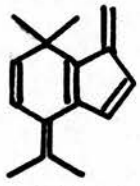
I

In contradiction to this, Ruzicka and Rudolph (Helv. Chim. Acta, 1926, 9, 118) found no trace of a benzene ring in the products of permanganate oxidation of azulenes. Hydrogenation or reduction produced compounds with molecular refraction corresponding to dicyclic sesquiterpenes, and the original azulene was regenerated by dehydrogenation. Ruzicka and Rudolph concluded that the colour of azulenes is conditioned by a particular grouping of five double bonds in a dicyclic structure, corresponding closely to, if not identical with, the sesquiterpene skeleton, and containing no aromatic ring. The ring system itself was not thought to be responsible for colour,

but to serve as a skeleton in which the facile rearrangements of the double bonds could occur which cause the difference from the isomeric naphthalenes, e.g. cadalene obtained from dehydrogenation of other sesquiterpenes.

From a study of azulene picrates from a number of oils, Ruzicka and Rudolph found only two azulenes, chamazulene and guaiazulene. The ultra violet spectra of both were determined and found to be identical. Hence it was considered that comparison by means of spectral determinations was invalid. This is not, however, true in the wider sense.

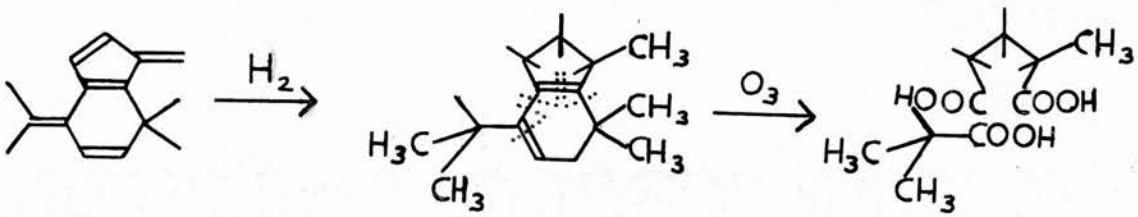
The use of sulphur and selenium to dehydrogenate guaiene was shown by Ruzicka and Haagen-Smit (Helv. Chim. Acta, 1931, 14, 1104) to give different azulenes, named sulphur- and selenium-guaiazulenes. Since ozonisation of sulphur-guaiazulene yielded acetone, acetic acid, formic acid and isobutyric acid, the formula II was considered possible.



II

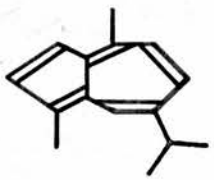
Melville (J.A.C.S., 1933, 55, 3288), who reacted guaiazulene with sodium and carbon dioxide, obtained an acid, $C_{30}H_{36}(COOH)_2$, which with ozone formed formaldehyde and formic acid but no

acetone. He concluded that the sodium attacks the isopropylidene group of the structure II. He found that the rate of hydrogenation of guaiazulene with palladium decreased greatly after reduction of 3.5 → 3.7 ethylenic linkages. The product of hydrogenation to the point of loss of colour, corresponding to reduction of 2.7 double bonds was ozonised by Birrell (J.A.C.S., 1935, 57, 893) in an attempt to isolate bigger fragments. He obtained formic acid, isobutyric acid, $C_{14}H_{21}COOH$ and α-methyl glutaric acid, which supported the structure proposed by Ruzicka and Haagen-Smit.

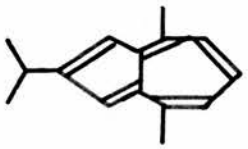


In 1936 Pfau and Plattner (Helv. Chim. Acta, 1936, 19, 858) critically reviewed previous work in the light of preliminary experiments on the parent sesquiterpenes. These indicated the presence of a seven-membered ring and led them to propose a structure with a bicyclo-(0:3:5)-decane system for the sesquiterpene and for the derived azulene. In a series of subsequent papers details were given of the facts leading to this conclusion. These have been reviewed by Simonsen (The Terpenes, Vol.III, Cambridge University Press, 1951).

Pfau and Plattner (Helv. Chim. Acta, 1936, 19, 858) first synthesised an azulene, 4-methyl-azulene, by reaction of methyl magnesium iodide with 2:3-tri-methylene- Δ^2-cycloheptenone and dehydrogenation of the product. They considered guaiazulene to be 1:4-dimethyl-7-isopropyl-azulene, III, and another naturally occurring azulene, vetivazulene, to be the 4:8-dimethyl-2-isopropyl derivative, IV. They were converted to different dimethyl isopropyl naphthalenes by heating over silica gel in vacuo.



III

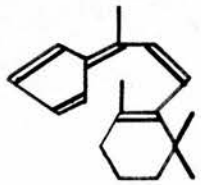


IV

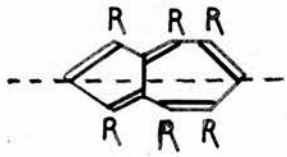
The parent substance, azulene, was synthesised in 1937 by Pfau and Plattner (Helv. Chim. Acta, 1937, 20, 224) from cyclopenteno-cycloheptanone. In the same year they isolated it from the product of dry distillation of calcium adipate. This had been done by Hentzschel and Wislicenus in 1893 (Ann., 275, 312) although the product was not identified. Pfau and Plattner also introduced the use of chromatography on alumina for purification of azulenes, and decomposition of their picrates and trinitro benzene complexes.

Guaiazulene, vetivazulene and synthetic unsubstituted azulene had their absorption spectra determined between 230 mμ and 750 mμ by Susz, Pfau and Plattner (Helv. Chim. Acta, 1937, 20, 469). It was found that the curves were very similar and that a practically constant difference exists between the frequencies of the maxima of azulene itself and guaiazulene in the visible region. In the ultra violet region, all three are very similar. This was regarded as confirmation of the presence of the bicyclo-(0:3:5)-deca-1:3:5:7:9-pentaene grouping.

In 1941, Plattner published a classical paper on the absorption spectra of azulenes (Helv. Chim. Acta, 24, 283E). He pointed out that their colour cannot be predicted from comparison with other hydrocarbons. Considering the fulvene, V, with the same number of double bonds, isolated by Willstaedt from β-ionone, he pointed out that by ring closure to azulene, the maximum is shifted to longer wave-length by 200 mμ. He concluded that azulene had a hitherto unknown type of system. Using the method of Slater and Pauling, Sklar calculated the position of the first maximum of benzene, fulvene and azulene as mesomeric systems and obtained good agreement with experimental. Thus the formula (chemically derived) having five conjugated double bonds in a continuous system was considered correct.



V



VI

Plattner put the alkyl substituted azulenes into three spectral classes:

(1) Those with no 2- or 6-substituent. Such substances, represented by formula VI, have almost identical banded spectra with a nearly constant difference of about 730 cm^{-1} between the frequencies of individual bands in the spectrum. The distribution of the intensities of the bands in the individual series is the same, the first, third and fifth being relatively the strongest. The bands of different alkyl azulenes are sometimes shifted relative to one another. Plattner found that a constant additive difference occurred on alkyl substitution in positions 1, 7 and 8, or the equivalent (3, 5 and 4) positions. The effect was independent of size of substituent.

(2) 2-substituted azulenes. These were shown to have a greater number of well marked bands with the first maximum shifted by +700 to 800 cm^{-1} from that of azulene itself. The fact that the size of the alkyl substituent did not affect this was doubted by Wagner-Jauregg, Arnold, Hüter and Schmidt (Ber., 1941, 74, 1522) but confirmed by Plattner and Fürst (Helv. Chim. Acta, 1945, 28, 1636). The effect of further substitution in positions 4 and 8 was the same as that of 4:8-dimethyl substitution in azulene. The spectrum of selenium-guaiazulene was found to be very similar to that of vetivazulene which was known to be 2-substituted. It was therefore deduced that migration of the 1-methyl group to the 2 position had

occurred during dehydrogenation with selenium. Fewer flatter bands were noted in these two compounds than in mono-2-substituted azulenes, but Plattner could find no explanation for this.

(3) 5-methyl azulene. This has a shift compared with unsubstituted azulene as expected from the findings for group (1), but since the intensity of the bands differs, it was put in a separate group along with 1:2-dimethyl-azulene, which is rather different from all other alkyl azulenes examined.

In the same year, Wagner-Jauregg, Arnold, Hüter and Schmidt (Ber., 1941, 74, 1522) determined the spectrum of an azulene containing a functional group, 2-ethyl-6-carbethoxy-azulene, and showed that the effect of this 6- substituent was to shift the absorption towards red compared with 2-ethyl-azulene. 2-Ethyl-4-methyl-8-methoxy-azulene was found to be lilac in colour. A 6-carbethoxy compound was hydrolysed (to 4:8-dimethyl-azulene-6-carboxylic acid) by Plattner and Roniger (Helv. Chim. Acta, 1942, 25, 1077) and then converted to its methyl ester. All three formed blue solutions, whereas 4:8-dimethyl-azulene is violet. Therefore the free carboxyl group in the 6 position is similar to the ester in producing a shift to longer wave-length. In contrast, an ester of a pentacyclic azulene-6-carboxylic acid prepared from 1:2-,3:4-dibenzfluorene by Ziegenbein and Treibs (Ann., 1955, 595, 203) is green, while the acid is blue.

The same workers in the following year (Helv. Chim. Acta, 1943, 26, 905) stated that alkyl substitution in the 6 position is found to be in group (1) with a shift of +355cm^{-1}, and, in general, that alkyl substitution in alternate positions in the azulene nucleus produces shifts in opposite directions, although the 2 position has a rather different effect from the others. They suggested that this observation might be used in determination of structure. A recent example is of zier-azulene which has spectrum similar to vetivazulene (Birch and Collins, Chem. and Ind., 1955, 1773) from which it was concluded that it is alkylated in the 2:4:6- or 2:4:8- positions. The regularity of the spectrum of 1:3:4:8-tetramethyl-azulene confirmed the absence of abnormality due to steric hindrance (Plattner, Fürst and Schmidt. Helv. Chim. Acta, 1945, 28, 1647). 1:2:3-Trimethyl-azulene was put into group (3) with 1:2-dimethyl-azulene, since the number of their bands is intermediate between groups (1) and (2).

The ultra violet spectra of alkyl mono- and poly-substituted azulenes were determined by Plattner and Heilbronner (Helv. Chim. Acta, 1948, 31, 804). All five monomethyl azulenes show shift of the spectrum to longer wave-length compared with the parent substance as in alkylated benzenoid compounds. This is in contrast to the spectra in the visible region, and the effects are not additive. This makes determinations in the ultra violet of less value but they may be used to determine the identity of

azulene samples. However a marked difference between the spectra of five- and seven-membered ring substituted azulenes was noted. Those of compounds substituted in the seven-membered ring strongly resemble that of the parent azulene. The introduction of unsaturated groups or conjugation with the ring, as in 2-phenyl-azulene, was found to give new character to the spectrum.

Günthard and Plattner (Helv. Chim. Acta, 1949, 32, 284) extended spectral measurements to the infra-red region. Little success has attended attempts to generalise the effect of individual substituents.

Plattner, Heilbronner and Weber (Helv. Chim. Acta, 1949, 32, 574) investigated the acid extraction process of Sherndal. They concluded from the colour change of the solution to orange in acid that it is not a simple solution process but a reversible reaction between the azulene and the acid. They extended the method of countercurrent distribution of Craig (J.Biol.Chem., 1943, 150, 33, and 1944, 155, 519) and Bush and Densen (Anal. Chem., 1948, 20, 121) to azulenes between organic solvents and mineral acids. The determination of the Hammet function, i.e. the acid concentration which extracts half of the azulene from the organic phase, was introduced by them as a physical constant which may be used to identify less than 1 mg. of an azulene with accuracy. Unsubstituted azulene was found to have a lower value than those of methyl substituted azulenes, and the order

of their values is retained though the values are altered when different acid/solvent systems are employed. It was found that the larger the substituent in a given position, the lower is the Hammet function, i.e. the higher the acid concentration required to extract the azulene. Plattner, Heilbronner and Weber pointed out the value of this, since spectral determinations give only the position and not the nature of alkyl substituents. The relation between the fraction extracted and the acid concentration was found to differ in the case of azulenes with unsaturated substituents. They extended the use of acid extraction of azulenes (Helv. Chim. Acta, 1950, 33, 1663) by stepwise dilution, resulting in fractional regeneration of the components of a mixture in order of increasing basicity. The value of the method for examination of the purity of an azulene sample was demonstrated.

Plattner, Fürst, Gordon and Zimmermann (Helv. Chim. Acta, 1950, 33, 1910) studied the rearrangement of the phenyl group in 1-phenyl-bicyclo-(0:3:5)-decadiene to the 2 position during dehydrogenation to the corresponding azulene. The migration was found to occur using sulphur at about 300° and using palladium/carbon above 320°. However, 2-phenyl-azulene was found to be converted to a slight extent to 1-phenyl-azulene by heating to 350°. They regarded this as evidence that the 2-substituted azulene must be the more stable.

In a lecture in August 1950, Plattner is reported (Ang. Chem., 1950, 62, 513) to have said that while azulene is considered to have strong aromatic character due to high resonance energy, most of the experimental work has been designed to show its unsaturated nature. It had been proved that there was no diene addition, auto-oxidation or polymerisation, but little attempt at direct electrophilic substitution which had been predicted as probable by R.D. Brown (Trans.Farad.Soc., 1948, 44, 984) from quantum mechanical investigations. Plattner attributed this lack of success to use of too violent conditions and described his experiments to couple diazonium salts with azulenes.

Anderson and Nelson in the same year (J.A.C.S., 1950, 72, 3824) described some preliminary work proving that electrophilic substitution does occur at the 1 position. 1-methylazulene, in minute amount, was prepared by the action of methyl chloride or iodide on azulene below room temperature, using aluminium chloride as catalyst. The authors considered that the compound formed using acetic anhydride with aluminium chloride is diacetyl azulene, and that from cupric nitrate and acetic anhydride, mono-nitro-azulene. An amorphous grey blue solid was obtained from the action of mercuric chloride on a solution of azulene in ethanol containing sodium acetate. The very rapid reactions are remarkable since the chloromethylation of thiophen takes several days.

This and the mild conditions required were regarded as indications that azulene is markedly more reactive with regard to electrophilic reagents than normal aromatic hydrocarbons or heterocycles.

Further data on the absorption spectra of azulenes substituted other than by alkyl groups was provided by Treibs and Stein (Ann., 1950, 572, 161 and 165). They prepared 1-methoxy and 1-ethoxy-azulenes and found that alkoxy substitution in the 1 position produces no shift towards longer wave-length in the visible region unlike alkyl substitution, and that the ultra violet spectra of 1-alkoxy-azulene and azulene itself are very similar. Thus they concluded that introduction of an alkoxy group has no great influence on the electron distribution of the azulene system. On the other hand, Ziegenbein and Treibs (Ann., 1955, 595, 211) have found that there is a bathochromic shift in the ultra violet region and a hypsochromic shift in the visible region on substitution of a 6-methoxy group in both 1:2-benzazulene and the ester of 1:2-benzazulene-5-carboxylic acid. In the first case, the hypsochromic shift is 15 mμ. They claim that their methoxy and dimethoxy azulenes have the same spectrum in the visible region as the parent azulene. The 4- and 5-methoxy-azulenes prepared by Stafford, Ward and Reid (Chem. and Ind., 1955, 1258) show hypsochromic and bathochromic shifts

respectively of 35 mμ compared with the parent azulene. 4-ethoxy-azulene was prepared by hydrolysis using ethanolic caustic potash of the ethyl 4-methoxy-azulene-6-carboxylate followed by decarboxylation. Similarly aqueous alkaline hydrolysis yielded 4-hydroxy-azulene-carboxylic acid. The lability of the alkoxy group is presumably due to the ease of nucleophilic attack in the 4 position, increased by the presence of the ester group, since replacement did not occur on unsubstituted 4-methoxy-azulene or on the ester from 5-methoxy-azulene-7-carboxylic acid. The stability of alkoxy azulenes to acid hydrolysis and the fact that a hydroxy azulene derivative could be isolated indicates that there is little tendency for a conversion from the azulene series to the tropone series.

Treibs and Stein also compared 1:2-benzazulene with azulene itself and found that a bathochromic shift occurred in the visible region, and a characteristic change in the ultra violet. Therefore addition of a benzene ring to azulene produces a profound effect on the system.

Treibs and Stein also described the compounds which they prepared by coupling diazonium salts to guaiazulene, chamazulene and 1:2-benzazulene. The indicator action over a low pH range was noted.

The absorption spectra of azulene carboxylic acids in the

infra red, visible, and ultra violet regions were studied by Plattner, Fürst, Müller and Somerville (Helv. Chim. Acta, 1951, 34, 971). In the infra red region those of the methyl esters of azulene-5- and -6-carboxylic acids were found to resemble those of 5- and 6-alkyl-azulenes, while the carboxylic acids have the expected lowering of the carbonyl frequency due to hydrogen bonding.

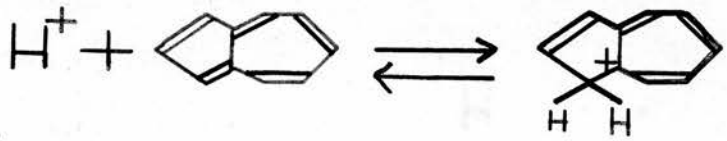
In the visible region, the data may be tabulated as follows:

Substituents	Spectral group	Shift
5-COOH	I	-15 mμ from azulene
2-methyl-5-COOH	II	- 7 mμ from 2-methyl-azulene
6-COOH	I	+55 mμ from azulene
2-methyl-6-COOH	II	+55 mμ from 2-methyl-azulene
5-methyl	I	+12 mμ from azulene
6-methyl	I	-15 mμ from azulene

J.P. Ward (private communication) has found that the spectrum of the sodium salt of azulene-6-carboxylic acid is not shifted from that of the free acid, although the maxima are higher. The salt appears more violet, but this can be attributed to higher absorption in the 440 → 590 mμ region.

In comparison with observations of the methyl azulenes, the introduction of a 2-methyl group into azulene-6-carboxylic acid shifts the ultra violet spectrum hypsochromically, and less, but in the same direction, in 2-methyl-azulene-5-carboxylic acid.

An important advance in the understanding of the azulenium system was made by Plattner, Heilbronner and Weber in 1952 (Helv. Chim. Acta, 1952, 35, 1036). They attributed the solubility of azulenes in mineral acids and the distribution between organic and acid phases to the formation of an azulenium cation, by addition of a proton. They represented this in the following manner



8 mesomers

A similar reaction was thought to occur with dry hydrogen chloride and solid guaiazulene. The colour of the solution changes to brown or reddish, and the absorption curve is smoothed out. This may be compared with other aromatic hydrocarbons in which the maximum shifts to longer wave-length in acid. The shape of the curve is the same for azulenium, guaiazulenium, and 2-methyl-azulenium ions. Therefore the proton was thought to add to the same position in each, and have the same effect on the electronic system. They also showed that the spectrum of a single ion is independent of the acid used, provided sufficient proton activity is present. Conductivity measurements

on azulenes in formic acid were used to detect that only one proton was linked to azulene. The basicity of azulene is described as being comparable to that of o- and p-nitroaniline. By use of the molecular orbital theory it was shown that the form of the cation given above has greater resonance energy if the proton is added at carbon atom 1.

The theory was extended by Heilbronner and Simonetta in Helv. Chim. Acta, 1952, 35, 1049. They regarded the azulenium ion as being similar to the transition state in an electrophilic or nucleophilic reaction on an aromatic system. In benzene derivatives the ion formation in acid is not measurable, but with azulene the conjugate acid shows comparatively little tendency to lose its proton, and the ion can be investigated. They concluded that of the possible azulenium ions, that with the proton added at carbon atom 1 (3) has the greatest resonance energy, the others are in equilibrium in only small amount. The shift of the maximum to shorter wave-length on acidification is only explained by formation of an ion of the form above. The abnormal basicity of azulene is explained by the greater resonance energy of the ion than of the hydrocarbon which is supported by wave mechanical reasoning.

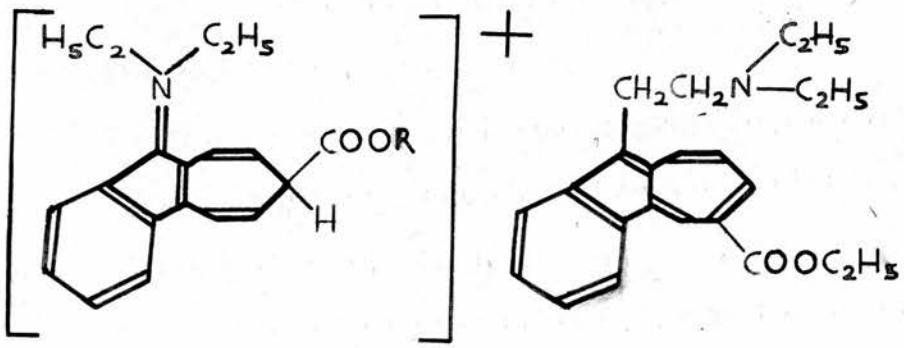
Chophard-dit-Jean and Heilbronner (Helv. Chim. Acta, 1952, 35, 2170)determined the position of the first maximum of 1- and 2- substituted azulenium ions. They were found to be shifted bathochromically in each case compared with that of

azulenium ion, and to lie between 350 and 370 mμ, i.e. the effect of 2-substitution in the ion is the reverse of that in azulene itself. A rough molecular orbital calculation for the eight principal possibilities of the methyl azulenium ions indicated that a hypsochromic shift would have been expected for 5-methyl- and 8-methyl-azulenium ions. This was shown experimentally for these and the ion from 4:7-dimethyl-azulene. Such shifts produced by alkyl substitution had previously only been known for azulenes, therefore another new molecular species was concluded to be under examination. The authors regarded the inductive and electromeric (hyperconjugative) effects of the substituents as being the cause of the shifts. The value of each for the different methyl substituted ions, and the equilibrium mixtures of ions (formed if proton addition occurred at C1 and C3 to give different but energetically possible ions) were calculated and agreed fairly well with the experimental values. The shifts and resonance energies of disubstituted azulenium ions were found by calculation and experiment to be additive.

The same authors carried out polarographic studies on azulene, the five methyl azulenes and di- and tri-alkyl-substituted azulenes (Helv. Chim. Acta, 1953, 36, 144). All showed many steps, the first corresponding to the consumption of a single electron by reduction. This is a property of some

non-alternant hydrocarbons. Alkyl substitution was found to move the half-wave potential in a negative direction as expected for a -I group, and the hyperconjugation did not affect this greatly. The effect of further substitution was again found to be additive.

A more significant electromeric effect was investigated by Treibs, Ziegenbein, Wetzel and Böhm (Ann., 1953, 577, 209) who prepared a green azulene by the action of diazoacetic ester on 9-diethylamino-fluorene. The spectrum of the picrate, and the ultra violet spectrum of the azulene corresponded to those of an ester of 3-diethylamino-1:2-benzazulene carboxylic acid. It was found to be more strongly basic than any other azulene known at the time. The position of the first maximum was at longer wave-length than 3-alkyl-substituted-1:2-benzazulenes, the expected effect of electron donation from the side chain to the ring. In addition the salt was formulated as VII which would involve diminution of the mesomeric possibilities and lowering the position of the maximum. The ultra violet spectrum of the azulene was similar to that of VIII.



VII VIII

Anderson, Nelson and Tazuma (J.A.C.S., 1953, 75, 4980) published a quantity of synthetic work which led them to represent the reacting structure of azulene as a resonance hybrid of two forms having six electrons in the seven-membered ring and a replaceable hydrogen at a negatively charged position exocyclic to the other ring. This is discussed later in the introduction (p.63).

They prepared mono-acetyl azulene by the action of stannic chloride and a large excess of acetic anhydride and reacted it with sodium hypochlorite. The product was not acidic, but di-chloro-azulene identical with that formed when N-chloro-succinimide was employed. However, using sodium hypoiodite, an acid was obtained which reacted with diazomethane yielding methyl-1-azuloate. This they had synthesised (J.A.C.S., 1953, 75, 4979), therefore unequivocal evidence was provided that acetylation had occurred in the 1 position. The spectra of mono-nitro-azulene was found to differ both in the ultra violet and in the visible regions from those of all other azulene derivatives. Azulene-azo-benzene was formed by reacting azulene with benzene diazonium chloride. Reduction of nitro-azulene or azulene-azo-benzene did not give the amino compound. Though some reduction occurred, it was not possible to diazotise and react the product with cuprous halide. N-acetylamino-azulene was prepared from both the above nitrogen-containing

compounds and from 1-acetyl azulene. Therefore they were both 1-substituted derivatives.

Immediate reaction without catalyst was observed to occur between azulene and N-halogeno-succinimides. The products were mono- and di-halogeno derivatives whose spectra resembled those of 1-alkyl and 1:3-dialkyl-azulenes. Attempts to convert them to carboxyl derivatives using magnesium, lithium, or n-butyl lithium were found unsuccessful. The same product was obtained from bromination of nitro-azulene and nitration of bromo-azulene, and this was converted to bromo-N-acetylamino-azulene, identical with that from N-acetylamino-azulene.

Anderson and his co-workers concluded that all compounds of proven structure resulting from electrophilic substitution are 1-substituted azulenes. They interpreted the formation of dichloro-azulene from the action of N-chloro-succinimide on 1-acetyl-azulene as involving electrophilic displacement by a positive chloride ion. The nature of the first group was not thought to affect the position of entry of the second group. All this was considered as good evidence for the aromatic character of azulene whose representation is outlined above.

Ukita, Watanabe and Miyazaki (J.A.C.S., 1954, 76, 4584) extended the work on acetylation of azulene to guaiazulene, obtaining 3-acetyl-guaiazulene using acetyl chloride or acetic anhydride. The acetyl derivative was treated with methyl magnesium iodide, yielding a tertiary alcohol which dehydrated

during chromatography on alumina to isopropenyl-guaiazulene. Catalytic hydrogenation, stopped after addition of one mole, produced a mixture of guaiazulene and its 2-isopropenyl and 2-isopropyl derivatives, i.e. migration occurred under very mild conditions. It was concluded that a tendency to rearrange occurs if an isopropyl group is introduced into the 3 position when the 4 position is already substituted.

Arnold (Ber., 1954, 87, 257) reduced the ethyl ester of 4:8-dimethyl-azulene-6-carboxylic acid to the alcohol which he converted to the 6-aldehyde. The alcohol in solution was deep violet (λmax. 649 mμ in petrol) and the aldehyde pure blue (λmax. 744 mμ in petrol) but green in the solid state. In the infra red region, the alcohol was found to have a typical alcohol absorption (3625 cm^{-1}), while the aldehyde has the carbonyl vibration frequency (1705 cm^{-1}) very strongly marked as in the ester. The absorption in the 760 → 740 cm^{-1} region is very similar to that of alkyl azulenes. Some esters did not reduce with lithium aluminium hydride to the corresponding alcohols. These were less symmetrical and were thought to be less stable and to polymerise through partial hydrogenation of the nucleus.

Treibs and co-workers have also published a number of papers on synthesis of azulenes containing functional groups. In their paper on the coupling of azulenes with diazonium salts

(Ann., 1954, 586, 194) Treibs and Ziegenbein studied this reaction as an example of electrophilic substitution. Crystalline products were obtained using phenyl diazonium chloride with guaiazulene or an ester of 1:2-benzazulene-6-carboxylic acid. Reductive splitting did not lead to isolation of the amino-azulene, but the original diazonium salt was regenerated. This was thought to be due to the instability of amino-azulenes to light and acid. By finding which azulenes did, and did not, couple with phenyl diazonium chloride, Treibs and Ziegenbein concluded that it does not occur if the 1 and 3 positions are already substituted. A single exception appeared to be 1:2:3-trimethyl-azulene.

The red or brown azulene-azo-benzene derivatives were more basic than the corresponding azulenes and showed the properties of indicators, adding a proton to form cations whose colour was characteristic of the diazonium component. From this it was concluded that only this part and not the azulene was responsible for the colour of the cation. The absorption in the visible region (λmax. 450 → 460 mμ) is therefore due to the conjugation of the aryl-azo group with the azulene part, while the nature and position of the substituents in the azulene nucleus have little influence. In acid, the maximum of the principal band of phenyl-azo-3-guaiazulene shifts to 540 mμ. In the ultra violet region the absorption curve was not found to

be characteristic of azulenes since, unlike the starting azulenes, the highest maximum was found to be in the visible region.

Sherndal's method for sulphonating guaiazulene (J.A.C.S., 1915, 37, 170) was improved by Treibs and Schroth (Ann., 1954, 586, 202) by using sulphur trioxide-dioxan adduct. The acid was isolated as the blue sodium salt, while the mother liquors, which were deep red, (from the ultra violet spectrum) contained another azulene which was not described further. The sodium salt of guaiazulene sulphonic acid is violet in water, and blue in alcohol. It was found that phenyl diazonium chloride couples fairly quickly, replacing the sulphonic group. Attempts to methylate it with dimethyl sulphate in alkali led to decomposition. However, the free acid, obtained from the sodium salt by use of hydrogen sulphide, was converted to the methyl ester with diazomethane. Both the acid and its ester were reversibly decolourised by dilute hydrochloric acid. While the sulphonic chloride, red in ether solution, and carmine to violet in petrol, was shown to be very unstable, the 3-sulphonamide was stable for a long time to concentrated hydrochloric acid. It was soluble in alkali giving a violet colour. Substituted amides were also prepared, but attempts to couple the sulphonic esters with phenyl diazonium chloride were largely unsuccessful.

In contrast to alkyl substituted azulenes, guaiazulene-3-sulphonic acid forms a brightly coloured salt by addition of a

proton in very dilute mineral acid. Treibs and Schroth explain the acid catalysed saponification of its ester by concentrated hydrochloric acid also in terms of addition of a proton to the nucleus.

The sulphonic group has little influence on the ultra violet spectrum. A characteristic difference was found for the sodium salt in 5N hydrochloric acid. Its first absorption band lies 10mμ to longer wave-length than in neutral or aqueous solution, i.e. it corresponds to that of guaiazulene. Greater differences in the bands of the sulphonic chloride express the more polar character of the molecule. Treibs and Schroth interpreted their findings as follows. The sulphonic group, in all its modifications, is hypsochromic in effect, being a short electrophilic chain. This was increased in aqueous solution of the acid and its salt in consequence of ionic dissociation. The position of the first maximum of the sulphonic acid, the amide, and the chloride lie in order of decreasing wave-length. The sulphonic chloride, when dissolved in a polar solvent, had the most powerful hypsochromic effect as expected. It was concluded that this considerable hypsochromic influence of groups not fixed directly to the azulene nucleus, but to the positively charged sulphur atom, alters the polarisation strongly as they are all electro-negative. Treibs (Angew. Chemie, 1955, 67, 76)

described nitration of azulene using nitric acid free from nitrous acid or with urea nitrate. Better yields were obtained from the esters of azulene carboxylic acids. He attributed this to the positive charge on the seven-membered ring being enhanced by the electro-negative ester group resulting in carbon atoms 1 and 3 becoming more negative. The position of substitution was found to be less specific than in other electrophilic substitutions although carbon atoms 1 and 3 are preferred. The nitro group is hypsochromic in effect, while the influence of the other substituents remains unaltered. All nitro-azulenes prepared were found to be reduced to the corresponding N-acetylamino-azulenes, cf. Anderson, Nelson and Tazuma (J.A.C.S., 1953, 75, 4980).

R.D. Brown (Trans. Farad. Soc., 1948, 44, 984; 1949, 45, 296; 1950, 46, 146) and Coulson and Longuet-Higgins (Trans. Farad. Soc., 1947, 43, 87; 1952, 47, 553) have considered radical substitution in azulene from the wave mechanical view point. Treibs considered that azulene treated with thermally decomposed diazomethane or diazoacetic esters is radically substituted, and obtained from guaiazulene and diazoacetic ester a guaiazulene acetic ester which could be converted to a methyl guaiazulene. The position of substitution proved to be in an even numbered position. He found that azulene could be alkylated by the Buchner reaction, showing a

similarity to benzene.

Direct substitution of alkyl and aryl groups in the 4 and 8 positions of azulene was successfully performed by Hafner and Welder (Angew. Chemie., 1955, 67, 302) using aluminium alkyls or aryls. This indicates that nucleophilic attack occurs at position 4 or 8.

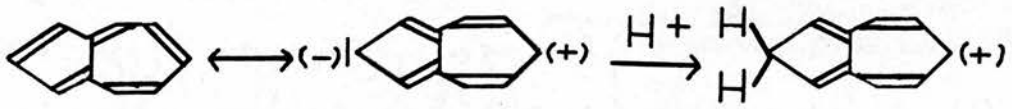
Further evidence is proved by reaction of azulene with sodamide (Stafford, Ward and Reid, Chem. and Ind., 1955, 1258) which yielded a nitrogen-containing compound whose absorption spectrum resembled that of their 4-alkoxy-azulenes.

Anderson, Cowles, Tazuma and Nelson (J.A.C.S., 1955, 77, 6321) extended their earlier work on alkylation of azulenes (Anderson and Nelson, J.A.C.S., 1950, 72, 3824) by using alkyl halides and aluminium chloride or bromide, but produced low yields of unidentified azulenic products. However, benzyl azulene was obtained using benzyl chloride and stannic chloride on azulene. It was identical with that synthesised by Anderson and Cowles (J.A.C.S., 1955, 77, 4617). Acetyl azulene was benzylated in the 3 position and the same compound obtained by acetylation of benzyl azulene.

A dichloromercuriazulene was isolated when azulene was treated with mercuric chloride and sodium acetate. The speed of formation was compared with that for heterocyclic ring systems, and azulene was considered to be more reactive to this reagent than thiophene and furan, and at least as reactive as pyrrole. Acetylation of this disubstituted azulene gave only 1-acetyl-azulene. No disubstituted products could be isolated to give the positions of attack by the mercuric chloride molecules.

Aza-azulenes:

In Ann., 1951, 574, 54, Treibs, Barchet, Bach and Kirchhof predicted that the substitution of a nitrogen atom in azulene would produce high intensity absorption bands without much change in the position of the maxima. This has not proved to be true for all the aza-azulenes of known structure so far isolated, none of which are blue. Treibs represented salt formation in azulene in the following manner:



(Ann., 1952, 576, ~~1952~~ 110)

The first aza-azulene to be prepared was 1-aza-2:3-benzazulene (Anderson and Tazuma, J.A.C.S., 1952, 74, 3455) by dehydrogenation of heptindole using palladium/carbon as catalyst. It is a dark red solid, basic in character, with ultra violet spectrum similar to that of 1:2-benzazulene and the maximum of the first band at 500 mμ. The structure of this compound was proved, while that of a blue solid claimed to be 1-aza-2:3-benzazulene which Treibs prepared (Ann., 1952, 576, 110) using iodine and nitrobenzene to dehydrogenate was not. It seems probable that the nitrogen had been lost from the ring during the dehydrogenation. Anderson and Tazuma using this

method obtained a red solid identical with that from the palladium/carbon method.

Treibs, Steinert and Kirchhof (Ann., 1953, 581, 54) further investigated 1-aza-2:3-benzazulene, finding it to be bluish-red in solution. It is strongly basic, and forms an orange salt by addition of acid. They prepared the methiodide (red needles) and the quaternary base which is colourless. They also prepared 1-aza-2:3-7:8-dibenzazulene as red needles, converted by acidification to a yellow salt.

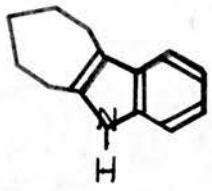
In the visible region, 1-aza-2:3-benzazulene has maxima at 550 and 507 mμ, i.e. it shows a large hypsochromic shift when compared with 1:2-benzazulene. The tetracyclic aza-azulene has its bands in the same place as the tricyclic one, but that at 550 mμ has much lower extinction, making the compound appear red. The large bathochromic shift in the ultra violet spectrum on addition of another benzene ring which is found in the carbocyclic azulenes also occurs.

The ultra violet spectra of the salts and methiodide of 1-aza-2:3-benzazulene show typical azulene spectra. The first band is in the same place as in the neutral substance, but in the quaternary cation the electron attraction from the ring is decreased, causing the curve to be smoothed.

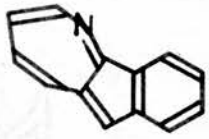
Lloyd (Chem. and Ind., 1953, 921) used chloranil to dehydrogenate 2:3-cycloheptanoindole, IX. He obtained, but

did not isolate, two products, one red, with maximum at 500 mμ, the other blue with maximum at 565mμ. The spectrum of the latter rather resembled that of the compound obtained by Treibs, Barchet, Bach and Kirchhof (Ann., 1951, 574, 54) by the action of diazoacetic ester on 4-aza-fluorene followed by decarboxylation. They claimed, purely by spectral evidence, that it was 4-aza-2:3-benzazulene, X, formed by attack on the pyridine rather than the benzene ring.

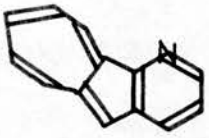
It seems more probable that 1:2-(2':3'-pyrido)-azulene, XI, would be formed, in view of the ease of attack by diazoacetic ester on benzene compared with pyridine.



IX



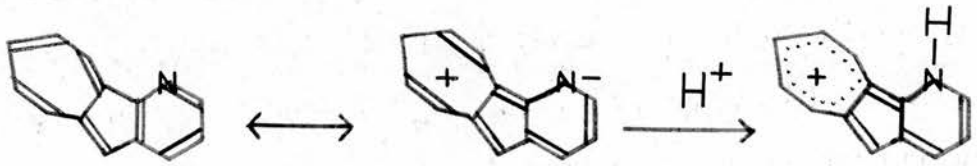
X



XI

Treibs and his co-workers regarded the extreme instability of the compound and its ester and the large hypsochromic shift in the maximum of the latter from that of the ester of 1:2-benzazulene-6-carboxylic acid as evidence for the 4-aza-2:3-benzazulene structure. From the fact that the ester forms a brown salt in acid, from which it is regenerated as a blue solid, violet in ethanol, it seems probable that is an

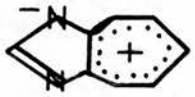
azulene substituted by the electron attracting pyrido group. The action of acid is represented as follows:



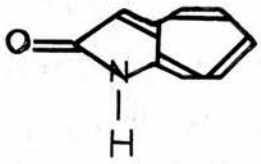
1:3-diaza-azulene was prepared by Nozoe, Mukai and Murata (J.A.C.S., 1954, 76, 3352). It is stable to acids, forming a dihydrochloride, and labile to alkali. Its dipole moment is 4.03D., and it is water soluble. The absorption in cyclohexane solution is above 500mμ but in more polar solvents it is shifted hypsochromically. Electrophilic substitution on a carbon atom, e.g. azo coupling and sulphonation, does not occur, instead it seems to form an addition compound with bromine. Nozoe and his co-workers regard this as indication of a large contribution to the resonance hybridisation of form XII.

Nozoe later, with Seto, Matsumura and Terasawa (Chem. and Ind., 1954, 1356) prepared 1:2:3-triaza-azulene which also did not undergo electrophilic substitution since positions 1 and 3 were occupied by nitrogen. They formed 2-hydroxy-1-aza-azulene from the tropone series, and found it to have quite a

different ultra violet spectrum from 2-methoxy-1-aza-azulene. This, with the infra red absorption, was considered to show that it exists in the 2-keto form, XIII.



XII

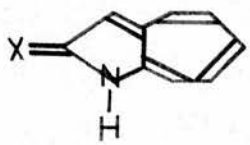


XIII

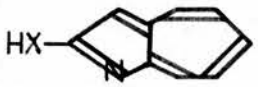
Since electrophilic substitution on a carbon atom does occur, it was assumed that it can react in the azulenic hydroxy form. The resulting bromo, nitro and phenyl-azo derivatives are all 3-substituted, and are red to yellow in colour. The latter two compounds may be reduced to the 3-amino derivative which is brown. The hydroxy or keto compound absorbs four moles of hydrogen, giving a colourless material.

From this 2-hydroxy-1-aza-azulene, the same workers (Chem. and Ind., 1954, 1357) prepared 1-aza-azulene, a red oil whose structure was ascertained from its ultra violet spectrum. Bromination occurs in the 3 position. The 3- and 2:3-halogeno derivatives are red, the 2-halogeno derivatives orange and the 2-amino and 2-methoxy derivatives yellow. Azo coupling does not occur under ordinary conditions, but the 2-dimethylamino derivative forms a red 3-p-tolyl-azo compound. From the

spectra it appears that the 2-hydrazino compound and 2-amino compound are of the 1-aza-azulan-2-one type, XIV, and the others of the 1-aza-azulene type, XV.

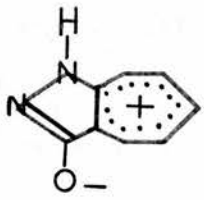


XIV

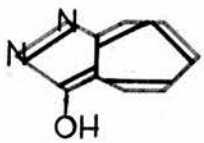


XV

Hunter, Lloyd, Marshall, Price and Rowe (Chem. and Ind., 1954, 1068) attempted to dehydrogenate 3:4-cycloheptano-pyrazol-5-one to 1-hydroxy-2:3-diaza-azulene, but realised that loss of oxygen might occur. Using palladium/carbon, and iodine and nitrobenzene they obtained two red violet compounds which they thought might be identical. They were soluble in water and not in non-polar solvents, gave a deep red-brown colour with ferric chloride and acted as indicators, red in acid, blue in neutral, and one violet and the other colourless in alkali. The properties indicate the highly polar nature of the molecule and they represented it as XVI, derived from XVII through acid ionisation of the hydroxy group by formation of the cyclohepta-trienylium ion.



XVI

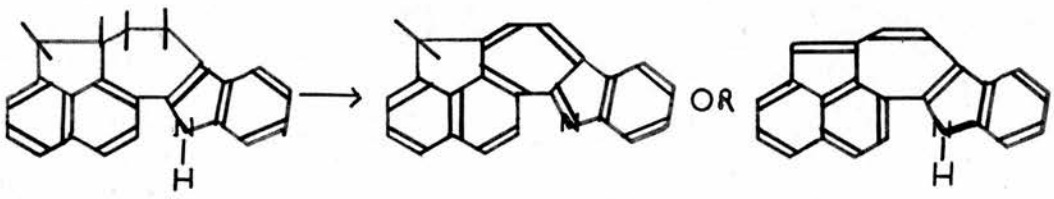


XVII

Heyer and Treibs (Ann., 1955, 595, 203) in the hope of preparing 4-methyl-1-aza-azulene by action of ammonia with furo-methyl-cycloheptadiene obtained a blue substance, which they identified as unsubstituted azulene, and naphthalene. Treibs has described all known aza-azulenes as red. (Treibs et al., Fortschritte der Chem. Forschung, Vol.III, p.367, [Springer-Verlag Berlin, Göttingen, Heidelberg 1955]).

They concluded that the azulene nucleus is energetically favoured in comparison with that containing a heterocyclic ring, and that it had a considerable tendency to be formed. Since ammonia does not convert furan to pyrrole, the evidence seems poor.

Ward (Ph.D. thesis. University of Edinburgh, 1956) attempted to prove whether an aza-azulene or a normal azulene structure was favoured by dehydrogenation of the substance XVIII. Unfortunately, the red "azulene" produced was too unstable to be investigated. This instability suggests that it may be an aza-azulene. The work was incomplete at the time of writing.



XVIII

Physicalchemical and wave mechanical data.

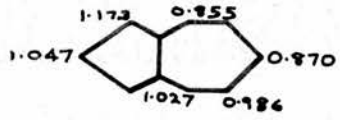
In order to differentiate the internal energy of the azulene and naphthalene systems, Perrottet, Taub and Briner (Helv. Chim. Acta, 1940, 23, 1260) determined the heats of combustion of the isomers, guaiazulene and cadalene, and found them to be 2022.9 and 1993.4 Kcal./mole respectively. The difference, 29.5 Kcal. is much greater than the experimental error. They calculated the heats of formation of azulene and naphthalene from atoms of carbon and molecules and atoms of hydrogen to be 367.2 and 396.7 Kcal./mole respectively. Therefore, they concluded that in passing from the naphthalene nucleus the bonding energy is diminished by almost 8%. This increased instability of azulene compared with naphthalene is in accordance with the findings using molecular models, and with the observed thermal rearrangement to naphthalene (Plattner and Wieland. Experientia, 1947, 3, 70).

The latest calculation of the resonance energy is that of Kovats, Gunthard and Plattner (Helv. Chim. Acta, 1955, 38, 1912) who obtained the values 46.8 Kcal./mole and 44 Kcal./mole for azulene and guaiazulene respectively.

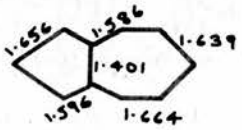
Wheland and Mann (J. Chem. Phys., 1949, 17, 264) gave the calculated value for the dipole moment of azulene as 1 → 2D. and the experimental value as 1.0 ± 0.05 D. Pullman and

Berthier (Compt. Rend., 1948, 227, 677) calculated the value as 5.25 D., later reduced to 3.8 D. (Compt. Rend., 1949, 229, 761). The experimental value of Wheland and Mann assumes that azulene has the same molecular refraction as naphthalene. This is therefore suspect, and the true value may be considerably higher than 1 D.

R.D. Brown (Trans. Farad. Soc., 1948, 44, 984) obtained values for the electron density at the carbon atoms, and the bond orders of azulene. They are represented in diagrams IXX and XX respectively.



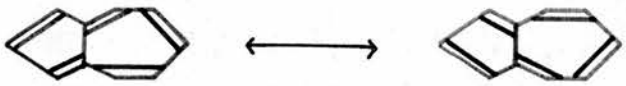
IXX



XX

Pullman and Berthier (Compt. Rend., 1948, 227, 677) also report values for the bond orders in which the common bond is of lowest order (and therefore the longest), and the others of approximately the same order, close to that of benzene, whose order is 1.667. Brown regarded this as not unexpected because consideration of the two most important structures, XXI and XXII, contributing to the azulene hybrid shows that all the bonds have approximately half double-bond

character except the bond common to both rings which is predominantly of single bond character. Approximately half double-bond character is also shown by the bonds of benzene, due to equal contribution to the hybrid of the two Kekulé forms.



XXI XXII

The X-ray evidence is not yet sufficiently refined to show if the common bond is shorter than a single bond (Gunthard, Plattner and Brandenberger. Experientia, 1948, 4, 425). The results of J.M. Robertson's X-ray study of azulene are awaited.

Brown also postulated from calculations of the polarisation energies at each of the five positions in azulene that electrophilic substitution would occur at position 1, and nucleophilic and radical substitution at position 4. This is in agreement with his highest value for the π electron density at carbon atom 1, and lowest value at carbon atom 4.

Sklar (J. Chem. Phys., 1937, 5, 669), attributing colour to transitions between levels which arise from a resonance among the different possible structures of a compound, calculated the position of the maximum of the first band of azulene. He used no optical data, only the heat of hydrogenation,

and arrived at 691.4 mμ as compared with the experimental value of 700mμ.

This band was compared by Mann, Plattner and Klevens (J. Chem. Phys., 1949, 17, 481) with the first band of the blue compound pentacene. It was found to have quite different properties. However, the observed energy levels in the azulene spectrum compared with the predictions of Coulson for the lowest states of naphthalene (Proc. Phys. Soc., 1948, 60, 257). Comparison of isomeric azulenes and benzenoid hydrocarbons was continued by Klevens (J. Chem. Phys., 1950, 18, 1063) using azulene and naphthalene, and 1:2-benzazulene and phenanthrene. The five band systems of each azulene correspond with regard to intensity, vibrational structure and sequence to the five in the isomer except that the former are shifted to lower frequency. The lowest frequency band is shifted some 17000 cm^{-1} to the red giving azulene its colour, whereas the four other transitions are shifted some 8000 - 9000 cm^{-1} compared with the regular isomers. Calculations of the positions of the five bands of azulene were published by Platt (J. Chem. Phys., 1950, 18, 1168).

Clar at this time (J.C.S., 1950, 1823) put forward the view that azulene exists as an equilibrium mixture of two forms, one of which is colourless, and the other, a more readily excited form, which is responsible for colour. Since its stability was thought to decrease with rise in temperature, he thought it might be a non-planar, "aliphatic" structure. Thus

the equilibrium was stated to be temperature dependent, and responsible for the observed variation in absorption spectrum with temperature. This alternative form is ascribed a diradical structure, but there seems little support for this belief. A more satisfactory interpretation is the betaine analogy which we have suggested (see later discussion). The variation of colour with temperature is also found in certain coloured substances examined recently by Hirshberg, Knott and Fischer (J.C.S., 1955, 3313) and by Saxena (Ph.D. Thesis. University of Edinburgh, 1955) where colour is related to the variation of solvent alignment with temperature.

Pullman, Mayot and Berthier (J. Chem. Phys., 1950, 18, 257) discussed the cause of hypsochromic shifts produced by methylating azulene in positions 2, 4 or 6. The usual bathochromic shift produced by alkylation of benzeneoid hydrocarbons they attributed to hyperconjugative and inductive effects. Since steric interference with co-planarity could not be claimed as the cause of the opposite shift in azulene, reasons were looked for in the structure itself and in the specific nature of interactions of the alkyl groups with the mobile electrons of the hydrocarbon.

In non-benzenoid hydrocarbons intramolecular charge displacement occurs causing a dipole moment. Pullman and his co-workers calculated the value of the charge density on the

different carbon atoms, obtaining values of the same order as those of R.D. Brown (Trans. Farad. Soc., 1948, 44, 984) and used them to evaluate the energies of the different alkylated azulenes.

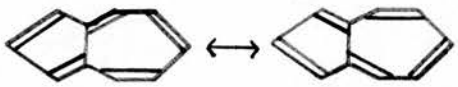
The bathochromic shifts for positions 1 and 5 were attributed to the usual differential raising of the energies of the ground and first excited state, the displacement being greater for the former. The hypsochromic shifts were considered to have two causes. In the 2 and 6 derivatives, displacement may be due to the fact that substitution does not bring about any appreciable change in the energy of the ground state, but only raises the first excited state. In the 4-derivative, they observed the customary change in both states, but in this case the excited state is raised more than the ground state. When their calculations were compared with experimental, they did not show good agreement.

Longuet-Higgins and Sowden (J.C.S., 1952, 1404) extended the work of Pullman, Mayot and Berthier by using an alternative method of calculation whereby the inductive and hyperconjugative effects were calculated separately. Qualitative agreement with the experimental values was obtained, and it was possible to predict a bathochromic shift on substitution in azulene at positions 1 and 5.

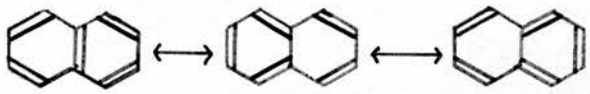
The positions of the first maximum produced by substitution of methyl groups in the 2 and 6, and 4 and 6 positions were also

calculated, assuming the effect in each position to be additive. This assumption was shown to be correct, the combined effect being due to the sum of the inductive effects only, since the combination of the hyperconjugative effects is zero.

Recent developments: Plattner proved azulene to be a cyclo-decapentaene and represented it as a resonance hybrid of two classical forms, XXIII (a) and (b), which correspond to those of naphthalene, XXIV (a), (b) and (c), to which it isomerises.



(a) XXIII (b)



(a) XXIV (b) (c)

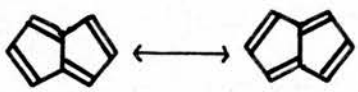
Each has ten π electrons. The resonance energy of azulene was found to be 46.8 Kcal./mole, in contrast to naphthalene, 77 Kcal./mole, and benzene, 39.4 Kcal./mole. The azulene molecule has indeed considerable stability shown by successful preparation by high temperature dehydrogenation of its hydro-derivatives. This tendency to be formed, and to undergo substitution rather than addition reactions may be regarded as evidence of aromaticity.

Robinson's concept of an "aromatic sextet" of mobile electrons as a necessity for aromaticity has since been extended

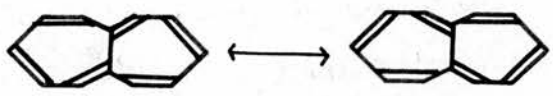
by Hückel, using molecular orbital theory, to $(4n + 2)$ 'π' electrons, where n = 0, 1, 2, 3, etc., for completely conjugated, planar, monocyclic polyolefins. No compound having a value of n other than 1 is known, but this supposition is of use in prediction of possible aromatic compounds. Although it is not applicable to polycyclic systems in which a bond is shared by more than two rings, azulene, with n = 2, does appear to meet the requirement. In addition, when a five- and seven-membered ring are fused, the external angle between the bonds at the ring-fusion carbon atoms is $124\frac{1}{2}^{\circ}$, very near that of a benzene carbon atom, therefore one would expect little strain to be imposed.

There are, however, three important properties of azulene which cannot be explained in terms of the above formulation, XXIII (a) $\longleftrightarrow$ (b). They are the dipole moment, colour and basicity.

Azulene may be considered as related to pentalene, XXV (a) and (b), and heptalene, XXVI (a) and (b).



(a) XXV (b)



(a) XXVI (b)

Armit and Robinson (J.C.S., 1922, 828) postulated pentalene as a possible aromatic compound, but later decided against this because there cannot be a sextet of π electrons in each ring. All attempts to prepare it have failed, but a non-aromatic unstable 1:2:4:5-dibenzpentalene was isolated by Blood and Linstead (J.C.S., 1952, 2263) who found it to react as a conjugated diene. Heptalene, XXVI, consisting of two fused seven-membered rings and containing six double bonds was suggested by Baker, Boarland and McOmie (J.C.S., 1945, 1476) as an example of a non-benzenoid aromatic compound. It also has not so far been prepared. During dehydrogenation of partly reduced compounds derived from bicyclo[5:5:0]-dodecane there was some evidence of ring contraction to derivatives of azulene and naphthalene, and Horn and Rapson (J.C.S., 1949, 2421) concluded that heptalene synthesis shows such difficulty that it is unlikely to be stable or aromatic in character.

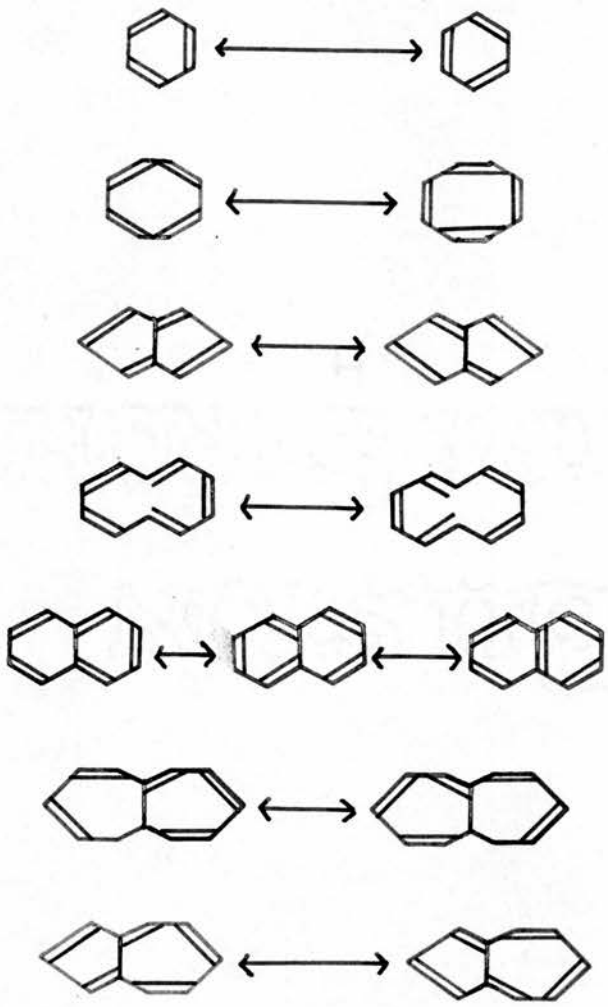
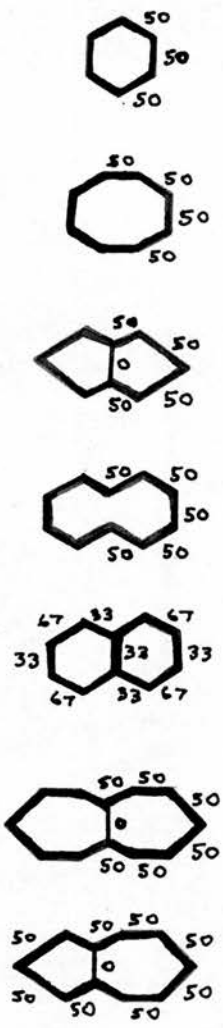
Baker and McOmie in their review of "Non-Benzenoid Aromatic Compounds" [Progress in Organic Chemistry, Vol.III Page 76. Butterworths] discuss this lack of aromaticity and attribute it to the fact that each ring possesses five π electrons unshared with the other ring and two which are shared. This gives a complement of seven to each ring which should be contrasted with the case of naphthalene which has six to each

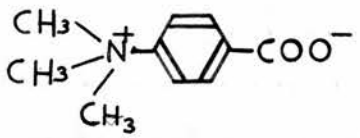
ring, four unshared and two shared. This view is open to a serious criticism.

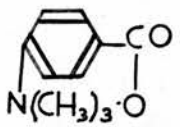
If the structures of pentalene, azulene, heptalene and related compounds are analysed, table I, using the valence bond method, it becomes apparent that the π electron distribution in each is not comparable. Only in the case of naphthalene can a form be written with a double bond at the ring junction, signifying some π electron density. Therefore only in it can trans-annular π electron fusion ("sharing") occur. The bond at the ring junction in the other compounds is purely single , conferring rigidity, but leaving them as cyclopolyolefins with corresponding properties. Since naphthalene is aromatic, unlike pentalene and probably heptalene, this trans-annular π electron fusion must be essential for aromaticity. Thus for azulene, which appears to be aromatic, we must propose a structure which fulfils this requirement.

The unexplained properties of azulene are comparable to those of anhydro salts which are reviewed by Saxena (Thesis. "Studies on Anhydro Salts". University of Edinburgh, 1955.)

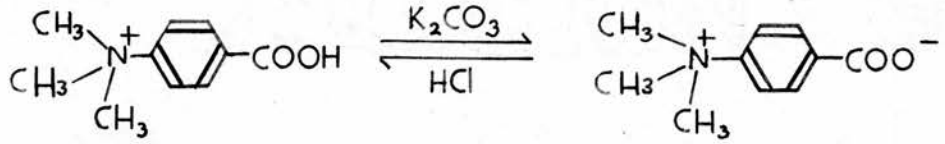
In 1922 Pfeiffer (Ber., 1922, 55, 1762) proposed an internal salt structure, e.g. XXVII (a) for such compounds, instead of the previous formulation, XXVII (b), involving a nitrogen atom linked by five bonds.

VALENCE BOND FORMS	HYBRID (% double bond)
	



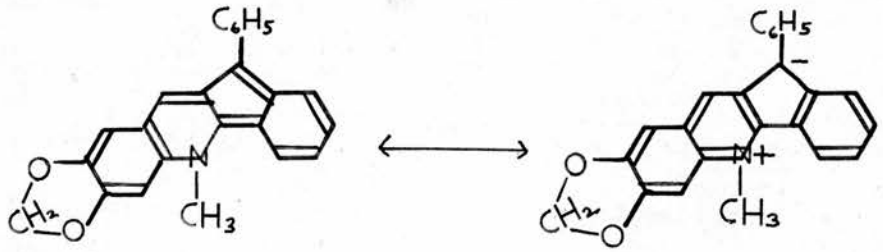
(a) XXVII  (b)

These substances formerly known as betaines are derived from cationic compounds possessing an acid group, or a group capable of acting as an acid, by loss of a proton. Pfeiffer represented the formation of XXVII (a) as

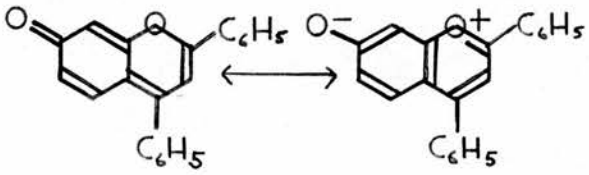


XXVII (a)

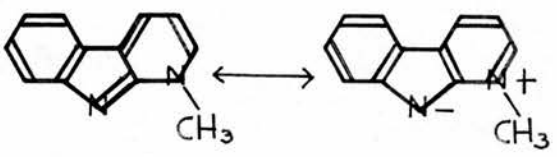
Armit and Robinson (J.C.S., 1925, 1604) used charged structures to describe compounds XXVIII, XXIX and XXX,



XXVIII



XXIX

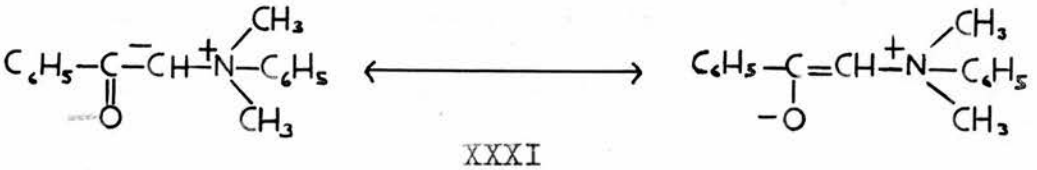


XXX

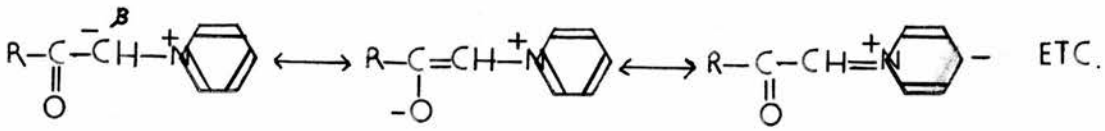
i.e. they represented them respectively as consisting of C betaine, phenol betaine and N betaine forms. They regarded them as a class of substances normally occupying an intermediate position between a fully polarised aromatic system and a neutral quinonoid system; anhydro derivatives of aromatic onium hydroxides.

The colour found in some of these anhydro salts was attributed by Krohnke (Ber., 1935, 68, 1177) to the composite effect of the extended conjugated system and the polar nature of the molecule. These two characteristics were subsequently interpreted in terms of the theory of resonance as causing a greater number of canonical forms of equivalent energy than are possible in a purely covalent compound.

Stafford (J.C.S., 1952, 580) has pointed out that in the enol betaines with a nitrogen atom as the cationic centre, only those with the nitrogen in a conjugated ring system are coloured, e.g. XXXI is colourless and XXXII is yellow. He concluded that for colour, resonance must be possible throughout the molecule.



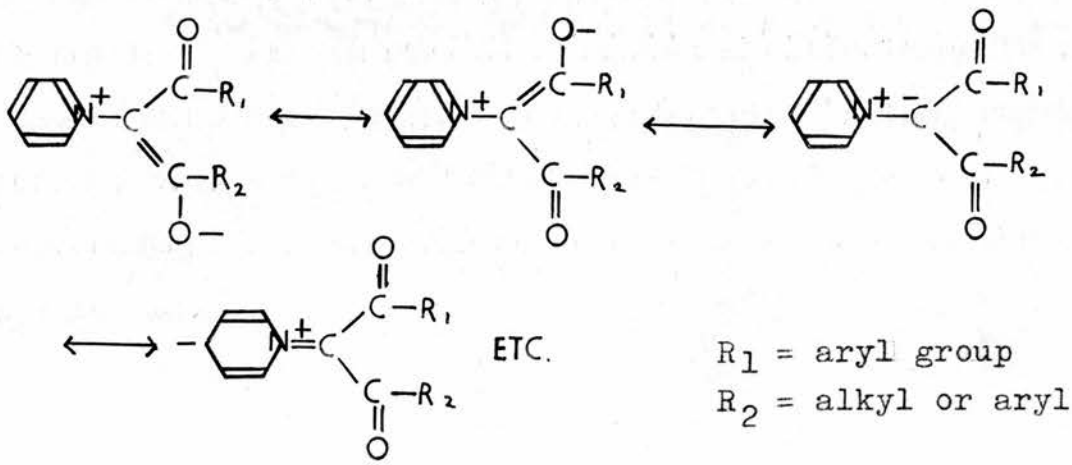
XXXI



XXXII R=CH_3 XXXIII R=C_6H_5

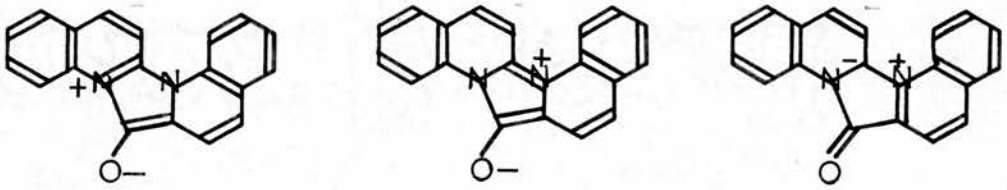
The difference in colour when quinolinium or isoquinolinium cations are used in place of pyridinium in XXXII must be related to the different contributions from their canonical forms.

Krönhke (Ber., 1935, 68, 1177) also produced chemical evidence for the charged structure of his phenacyl pyridinium anhydro salts, XXXIII, through the reactivity of the β-hydrogen atom, their basicity and hydrate formation. The fact that when the β-hydrogen atom is substituted by an acyl group, i.e. corresponding to general formula XXXIV, the compounds show greater stability, higher melting point and solubility in polar solvents, and no basicity was recognised as being due to increased mesomeric possibilities.



XXXIV

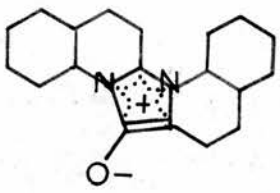
Krollpfeiffer and Schneider (Ann., 1937, 530, 34) determined the absorption spectrum of Besthorn's red (Besthorn. Ber., 1913, 36, 2762) in different solvents. (Scheibe. Angew Chemie., 1937, 50, 212). The hypsochromic shift in the visible region with increase in dielectric constant of the medium was used as evidence of its enol betaine structure, XXXV, through changes in the contributions of the various dipolar canonical forms.



(a) (b) (c)

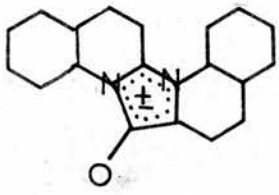
XXXV

They considered the forms XXXV (a) and (b) to be the most important, and introduced the representation XXXV (d) to denote the fact that the positive charge might be on either of the nitrogen atoms, and that one of the bonds in the five-membered ring had considerable double bond character. Hammick and Roe (Chem. and Ind., 1953, 900) regarded Besthorn's red as a "mesoionic" compound, XXXV (e), which means a resonance hybrid of a number of covalent forms, with no well developed charge on any one atom in the five-membered ring.



(d)

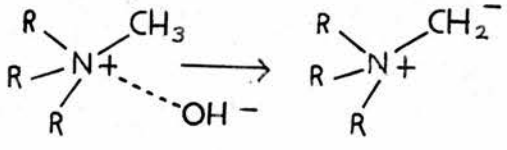
XXXV



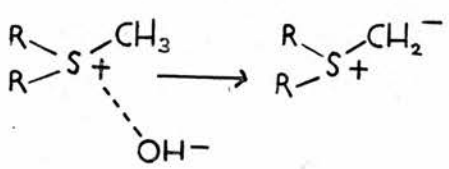
(e)

The term "mesoionic" and its representation with the symbol ± are now regarded with suspicion (cf. Katritzky, Chemistry and Industry, 1955, 521).

The blue colour produced by the action of alkali on fluorenyl-9-pyridinium salts, by analogy with betaine formation, was linked by Krollpfeiffer and Schneider (Ann., 1937, 530, 34) to the formation of an ylide. The ylides were reviewed by Wittig (Ang. Chemie, 1951, 63, 15). The name had been given by Ingold and Jessop (J.C.S., 1929, 2357; 1930, 713) to the coloured intermediates, XXXVI and XXXVII, formed in degradation of quaternary ammonium and sulphonium hydroxides.



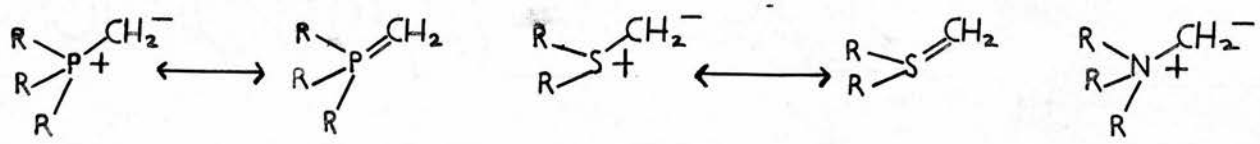
XXXVI



XXXVII

The name was intended to show the covalent (yl) and ionic (ide) nature of the semi-polar bond formed from a cationic compound by loss of a proton attached to a carbon atom. The ylides are in fact another name for the C betaines, e.g. XXVIII, of Armit and Robinson (J.C.S., 1925, 1604).

The photo-chemical instability of the ylides is due to the ease of oxidation of the carbanion by the atmosphere. This is found to a lesser extent in all anhydro salts. Stability, depending also on the energy of the dipolar molecule, increases with the rise in its mesomeric possibilities. Thus phosphonium and sulphonium ylides, XXXVIII (a) and (b) and XXXVII (a) and (b), are more stable than ammonium ylides, XXXVI.

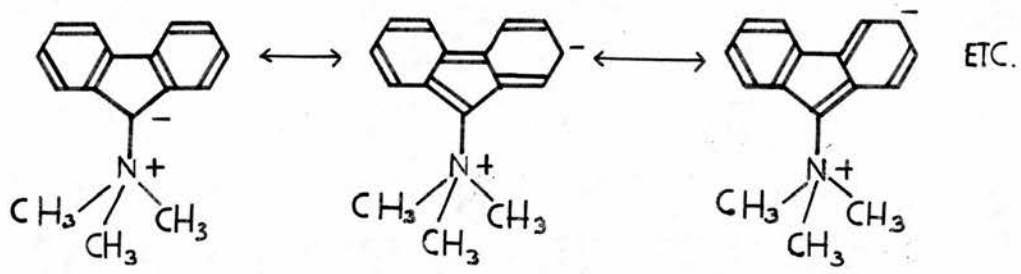


(a) XXXVIII (b) (a) XXXVII (b) XXXVI

Further evidence for dipolar character is the tendency of ylides to undergo rearrangements and addition reactions which may be explained in terms of the carbanion.

With the introduction of an aromatic anionic system, the

ylide becomes coloured (Lloyd and Sneezum. Chem. and Ind., 1955, 1221). Trimethyl-ammonium-9-fluorenylide is ochre yellow (Wittig. Ann., 1944, 555, 133). It may be represented by XXXIX (a) or by forms bearing the negative charge on any of the carbon atoms of the six-membered rings, e.g. XXXIX (b) and (c). Since XXXIX (a) is the only form to have both benzenoid rings in Kekulé form, it may be considered the greatest contributant.



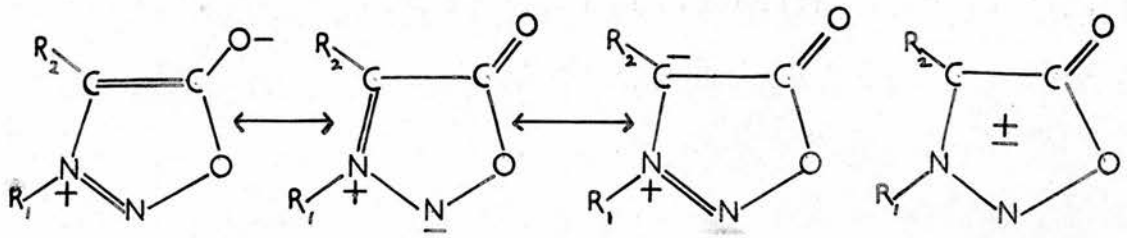
(a) (b) (c)

XXXIX

Clark and Stafford (University of Edinburgh, unpublished work) have observed a hypsochromic shift in the absorption spectrum of 2-nitro-pyridinium-9-fluorenylide with rise in the dielectric constant of the solvent.

The sydnones of Earl and Mackney (J.C.S., 1935, 899) and Eade and Earl (J.C.S. 1946, 591) are neutral, colourless anhydrides of N-nitroso-N-aryl glycines which could not be represented satisfactorily by a covalent structure. Although they have low melting points and are soluble in most organic

solvents including benzene, they have a high dipole moment, 6→7D. (Hill and Sutton, J.C.S., 1949, 746). From their determinations of the moment of the molecule and the chemical properties, these workers decided that the compounds were resonance hybrids, with XL (a), (b) and (c) as significant contributing forms.



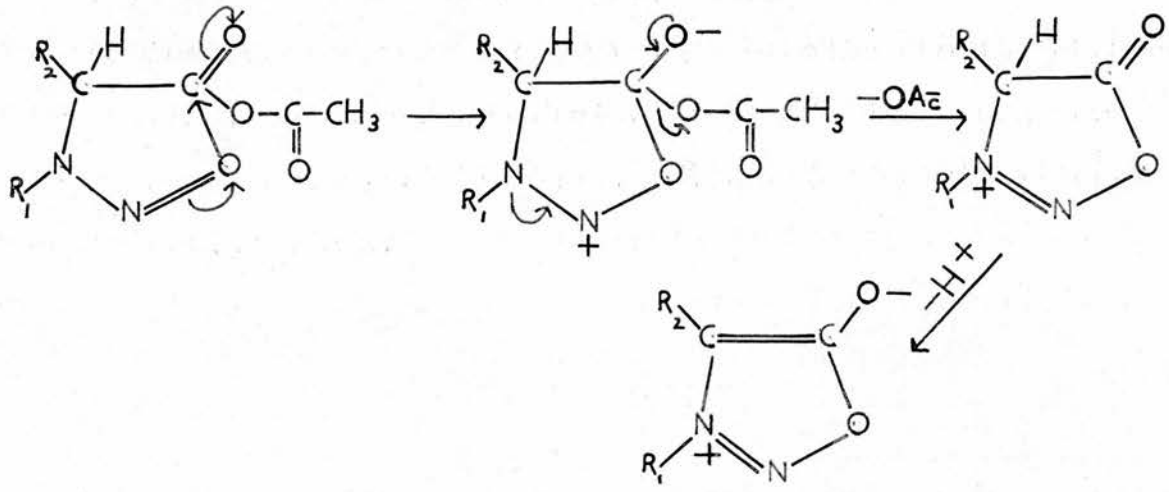
(a) (b) (c) (d)

XL

Baker, Ollis and Poole (J.C.S., 1949, 307) introduced the term "mesoionic" compounds with reference to these compounds, representing them as XL (d), and postulated a number of contributing forms including XL (a), (b) and (c). However, form XL (a), the enol betaine structure, would appear to be the most important, since the oxygen atom is the most, and the nitrogen atoms the least electro-negative in the system.

The lack of colour in a compound capable of representation in a number of canonical forms may be attributed to the fact that the molecular orbital envelops only one ring. The

mechanism for the formation of the sydnones put forward by Baker, Ollis and Poole (J.C.S., 1950, 1542)



at the last stage closely resembles that of an anhydro salt.

Since contributing charged forms appear to give rise to dipole moment, basicity and colour in anhydro salts, it was thought that a similar formulation might be applicable to azulene. This would necessarily involve the removal of an electron from one of the rings and donation to the other.

Molecular orbital calculations of the stabilities of the ions of three-, five- and seven-membered rings (Roberts, Streitwieser and Regan. J.A.C.S., 1952, 74, 4579) predicted that the cations of three- and seven-membered rings and the anion of the five-membered ring would be the most stable, which is in agreement with Hückel's requirements for aromaticity. These ions may be represented by formulae XLI, XLII, and XLIII,

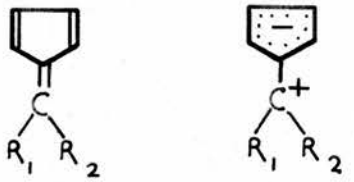


XLI XLII XLIII

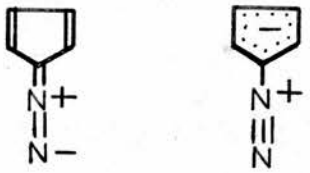
to indicate delocalisation of the charge throughout the system of cyclic molecular orbitals. These are composed of as many π orbitals as there are carbon atoms in the polygons, and are occupied by an equal number of electrons plus or minus the one indicated by the negative or positive sign. The charge is not necessarily distributed equally on each of the atoms in the ring.

Doering and Knox (J.A.C.S., 1954, 76, 3203) regard cyclopentadienylium anion, benzene and cycloheptatrienylium cation, each possessing six π electrons, as a triad of stable aromatic systems. The acidity of cyclopentadiene, resulting in formation of metallic salts containing the corresponding anion, has long been known. The difference in resonance energy between cyclopentadiene and its anion was calculated to be about 39 Kcal./mole (Roberts, Streitwieser and Regan. J.A.C.S., 1952, 74, 4579). In 1928, Gross and Ingold (J.C.S., 1928, 1268) had attributed this anionic stability to the distribution of six electrons, (a sextet), over five equivalent CH groups in analogy with

benzene, and Ingold and Jessop (J.C.S., 1930, 713) recognised its significance in the stability of the fluorenylides. It should be recalled that a simple ylide with a five-membered ring as anionic centre has recently been prepared by Lloyd and Sneezum (see p.52). The well known condensation of cyclopentadiene with aldehydes or ketones to form fulvenes, XLIV(a), is considered to occur through preliminary formation of the cyclopentadienylium anion. The dipole moment, resonance energy, and colour of the fulvenes (Review. "Progress in Organic Chemistry", Vol.III, Page 81, Butterworths) supports the possibility of contributions from the structures XLIV(b)



(a) XLIV (b)

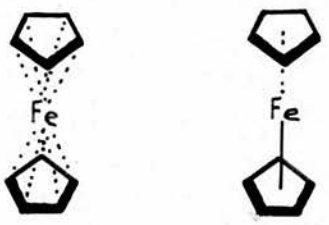


(a) XLV (b)

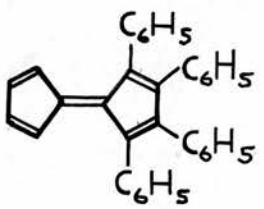
The cyclopentadienylium ion probably also occurs in diazocyclopentadiene, XLV (a) and (b) (Doering and Depuy, J.A.C.S., 1953, 75, 5955).

Ferrocene or dicyclopentadienyliron was thought by Wilkinson, Rosenblum, Whiting and Woodward (J.A.C.S., 1952, 74, 2175) to consist of two cyclopentadienylium anions forming covalent bonds with a ferrous ion. Later their interpretation

of the similarity of the first dissociation constant to that of benzoic acid (Woodward, Rosenblum and Whiting. J.A.C.S., 1952, 74, 3458) led them to the conclusion that there is no charge on the ring carbon atoms, and to describe ferrocene as a new type of aromatic system. They pictured the molecule as of general form XLVI(a). This formulation was supported by X-ray measurements (Eiland and Pepinsky. J.A.C.S., 1952, 74, 4971) which showed a symmetrical molecule in anti-prismatic form with the bond lengths of the five-membered rings as 1.40 Å, and Fe-C distance 2.0Å. Dunitz and Orgel (Nature, 1953, 171, 121) interpreted these findings by the presence of two 'covalent ionic' bonds and two 'donor' bonds in which the electrons of the iron atom spread into the empty cyclopentadienylium orbitals causing them to acquire negative charge. In his review (Quart.Revs., 1956, 391) Pauson prefers to regard the iron atom as linked by a single covalent bond, represented by XLVI(b).



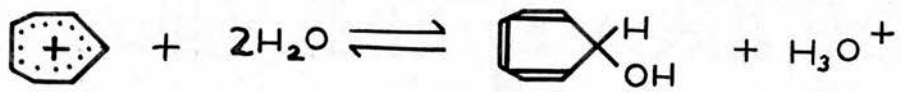
(a) XLVI (b)



XLVII

Although fulvalene cannot possess six π electrons in each ring, the preparation of its tetraphenyl derivative, XLVII, is claimed (Schreiber and Becker. J.A.C.S., 1954, 76, 3354).

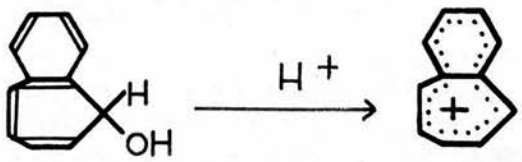
In support of their view of cycloheptatrienylium (tropylium) cation as an analogue of benzene, Doering and Knox (J.A.C.S., 1954, 76, 3203) prepared the bromide and found it to have considerable stability. (This was also claimed by Dauben - Abstracts of the American Chemical Society, 126th Meeting, 1954, p.18-O). When it was dissolved in water, equilibrium was set up between the ion, XLIII, and its pseudo base.



XLIII

The acidity in water was approximately that of acetic acid. Doering and Knox realised that the degree of stabilisation of the positive charge must be high in order to overcome the normal covalent tendency of the C-Br bond. It is interesting to note that the ion had been prepared by Merling in 1891 (Ber., 1891, 24, 3122) although its structure was not recognised. Salts of the benzotropylium cation, XLVIII, were isolated by Rennhard,

Heilbronner and Eschenmoser (Chem. and Ind., 1955, 415) using an alternative approach through the action of mineral acid on 3-hydroxy-1:4:6-cycloheptatriene.

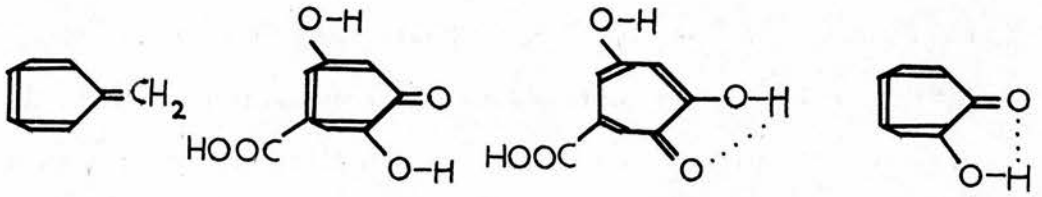


XLVIII

From studies of cycloheptatriene derivatives, Johnson, Langemann, and Tisler (J.C.S., 1955, 1622) found that the ethers, amine and urethane were all covalent compounds and concluded that for stability the tropylium ion needs an anion from a strong acid. This need for a strongly electro-negative group may explain the fact that 1-methylene-2:4:6-cycloheptatriene, XLIX, has resisted attempts to prepare it (Grundmann, Ottmann and Gollmer. Ann., 1953, 582, 178). However, if this methylene group is replaced by a more electron attracting oxygen atom, the resulting compound is the stable parent of the tropone series.

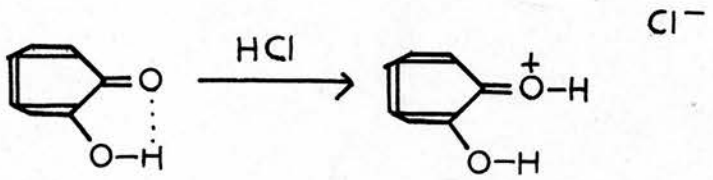
Dewar (Nature, 1945, 155, 50) was the first to postulate the presence of a seven-membered ring with a resonating system involving hydrogen bond chelation as a structure for the

compound stipitatic acid, L(a) and (b), which he regarded as containing a new type of aromatic compound with tropolone, LI(a) as parent.



XLIX (a) L (b) LI(a)

He recognised its amphoteric nature, and predicted that the salt formed in alkali would be red, and described that formed in acid as LII.

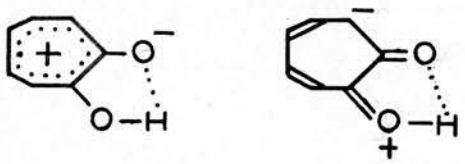


LII

Tropone and tropolone were reviewed by Pauson (Chem.Revs.,1955, 55, 9) and Johnson (J.C.S., 1954, 1331).

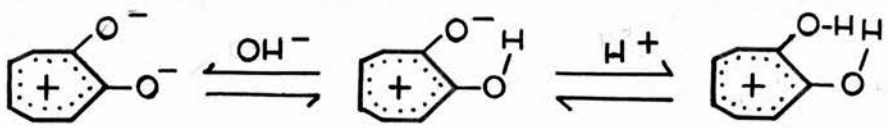
Tropolone is a stable compound and does not behave as a ketone or a polyolefin, but rather as a phenol, showing weak acidity (pk 7.0) and readily undergoes electrophilic substitution at the α and γ positions. In addition, its dipole moment was

measured as 3.71D. (Kubo, Nozoe and Kurita. Nature, 1951, 167, 688), and physical methods of analysis show it to be an almost regular heptagon of bond length 1.40Å (c.f. benzene 1.39Å) and to have the carbonyl group strongly conjugated with the ring. These properties, together with its amphoteric nature, led Doering and Knox (J.A.C.S., 1952, 74, 5683) to propose tropolone as a resonance hybrid with contributions from forms LI (a) and (b). To these Nozoe and his co-workers added a form LI (c) (Nature, 1951, 167, 688). His molecular orbital calculations showed the π electron distribution to be concentrated at the α and γ positions in the ring. Some workers regard tropolone as a cyclic vinylogue of a carboxylic acid with the corresponding directing influence to these positions with respect to electrophilic substitution.

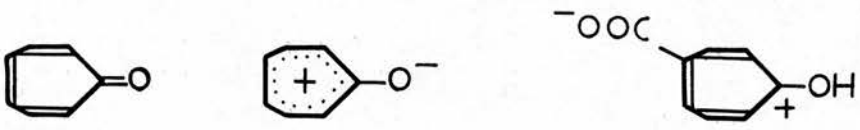


(b) LI (c)

The amphoteric nature was described as the following:



Aromatic character is also present in tropone, LII (a), which Dauben and Ringold (J.A.C.S., 1951, 73, 876) and Doering and Detert (J.A.C.S., 1951, 73, 876) synthesised to find the minimum structural features for resonance in a seven-membered ring. Dauben and Ringold, finding its properties similar to those of 4-pyrone, suggested that the aromatic character was due to an analogous carbonyl polarisation, LII(b), and resonance of six π electrons among the seven orbitals. Both groups of workers reached the conclusion that it should be represented as a resonance hybrid of LII (a) and (b), from consideration of the reversible formation of a hydroxy-cycloheptatrienylium salt with mineral acid, of the high boiling point and molecular refraction, its miscibility with water, low carbonyl activity and shifted carbonyl vibration frequency.



(a) LII (b) LIII

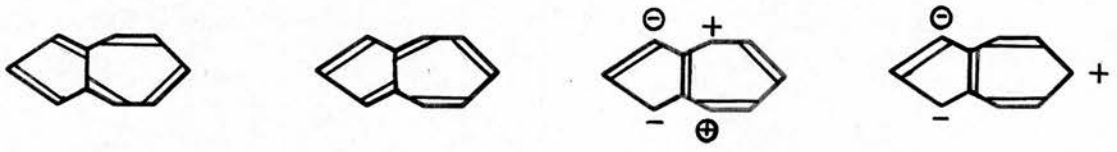
Tropone is regarded by some as a cycloheptatrienylium oxide from these properties and on theoretical grounds (Brown. J.C.S., 1951, 2670). It undergoes electrophilic substitution

reactions and there is evidence that its 4-carboxylic acid[LIII] has the properties of a zwitterion (Bartels-Keith, Johnson and Langemann. J.C.S., 1952, 4461). Values of 4.17 and 4.3D. have been obtained for the dipole moment of tropone. This is higher than that recorded for tropolone, but dipole moments of hydroxy compounds which are capable of association are not so simply interpreted. The existence of only two contributing forms would not be enough to give such aromaticity. The resonance energy, calculated to be at least 36Kcal./mole, must be due to the particular stability of a cyclic system containing six π electrons.

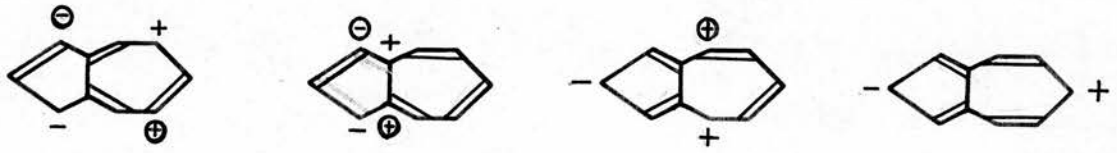
This evidence for the stability of the negatively charged five-membered ring and the positively charged seven-membered ring may be regarded as supporting the view that azulene has contributions from forms in which an electron is transferred from the seven-membered to the five-membered ring, giving six π electrons in each (Stafford and Reid. Chem. and Ind., 1954, 277; and Galloway,Reid and Stafford. Chem. and Ind., 1954, 724). Anderson, Nelson and Tazuma (J.A.C.S., 1953, 75, 4980) also reached this conclusion but from consideration of the aromaticity of the system shown by its substitution reactions.

The resulting resonance hybrid is derived from the following

nineteen canonical forms:



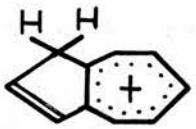
(a) (b) (c) (d)



(e) (f) (g) (h)

The two forms (g), and also (h), postulated by Treibs and co-workers (Ann., 1952, 576, 110), being quinonoid in nature, may be expected to be the least important. Six forms show some π electron density at the ring junction bond. Therefore the aromaticity of azulene is explained by this formulation, (p.44). It also supplies the reason for its dipole moment through charge separation, the electrophilic substitution at position 1 through the large contribution from forms with negative charge at this carbon atom, and also the colour.

The salts of azulene would be expected to consist of the cation LIV, formed by addition of a proton at the most negative position. This is in accordance with the evidence of Plattner, Heilbronner and Weber (Helv. Chim. Acta, 1952, 35, 1036, 1049 and 2170).



LIV

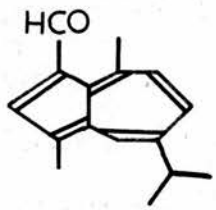
S E C T I O N A.

The object of the work described in this section was to prepare and study derivatives of azulene in which electron attracting groups have been introduced into position-1. Interest was focussed on the effect of the entering group on the typical azulenic properties and the reciprocal effect of the azulene nucleus on the properties of the entering group. Since guaiazulene (1:4-dimethyl-7-isopropyl-azulene) is commercially available, it was employed rather than the less readily obtainable parent, azulene. The substitution reactions with guaiazulene involve position-3 which is equivalent to a position-1 in azulene. The symbol Gu-3 is used to signify a guaiazulene nucleus substituted in the three position.

Routes to acyl guaiazulenes were first explored. Azulene has been reported to suffer mercuration readily (c.f. Anderson, Cowles, Tazuma and Nelson. J.A.C.S., 1955, 77, 6321), and by analogy with mercuri-derivatives of heterocyclic compounds, these would be expected to yield acyl compounds when reacted with acyl halides. Guaiazulene was found to react readily with mercuric acetate. When the reaction was carried out in glacial acetic acid solution, an orange colour was formed, but no pure product could be isolated since decomposition

occurred during the removal of the solvent. It was found however that a yellow aqueous extract of the mercuri-acetate could be made by shaking a solution of guaiazulene in petrol ether with a saturated aqueous solution of mercuric acetate. The mercuri-chloride was formed by treating the yellow solution of the acetate with an aqueous solution of an inorganic chloride. The solid initially precipitated was bright yellow, but in contact with the aqueous media it rapidly decomposed to guaiazulene. To obtain material in a comparatively pure form, it was found best to use barium chloride as decomposition was then minimal. The analysis showed that the compound was mixed with mercuric chloride but purification by washing with acetone caused decomposition. The mercuri-chloride was treated with benzoyl chloride, but no evidence of the presence of benzoyl guaiazulene among the products was obtained. The instability of the mercuri-compounds and the obvious complexity of the mixture of products led to abandonment of this method.

The next project was the synthesis of guaiazulene-3-aldehyde, LV, by the Gattermann method.



LV

This involved a study of the reaction of guaiazulene in different solvents with hydrogen cyanide, hydrogen chloride and zinc chloride (zinc cyanide and excess hydrogen chloride). In a preliminary experiment when methylene dichloride was used as solvent, it was observed, before addition of zinc cyanide, that the solution changed from blue to colourless during saturation with hydrogen chloride. This observation led to the second section of the thesis. The best results in the Gattermann reaction were obtained using dry ether as solvent. A red complex separated which on decomposition with acid gave unchanged guaiazulene and a red aqueous solution. The latter became blue when it was made alkaline, and formed a blue extract in ether, leaving a purple aqueous phase. The coloured material was removed from this by a second extraction with ether. When the solvent was removed from the combined extracts by distillation, extensive decomposition occurred, presumably due to concentration of peroxides present in the ether. However, after an ethanolic solution of the reagents required for the formation of a 2:4-dinitrophenylhydrazone or oxime was added and the ether removed, the corresponding derivatives with the correct analyses were obtained.

The oxime material although crystalline melted over a wide temperature range. Rechromatography separated it into two fractions (designated aldoxime I and aldoxime II) which had

different crystalline forms, melting points and absorption spectra. The total yield of oximes was 37%, of which less than 3% appeared to be in form II. The compounds were thought to be the two stereoisomers of guaiazulene-3-aldoxime, or, less probably, structural isomers. During distillation of the solvent from aldoxime I fractions, fine yellow/green needles were deposited on the walls of the flask above the level of the solution. This was true even of fractionally sublimed aldoxime I. However, the spectrum of solutions of the yellow/green solid was found to be the same as that of aldoxime I, with no absorption of blue light due to the presence of yellow material. The other properties investigated appeared to be those of aldoxime I of which it may be a second crystalline modification.

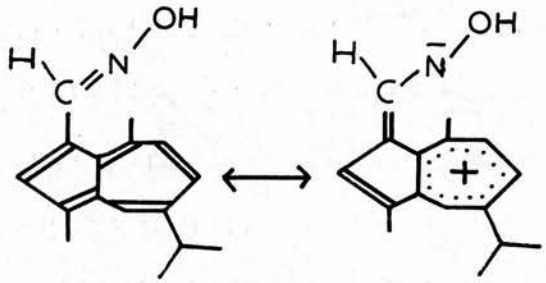
Solid hydrochlorides of both aldoximes were obtained. Each was unstable and could not be recrystallised. That from aldoxime I was initially red, but turned in part to purple on the filter. It decomposed in alkali to aldoxime II. The purple hydrochloride from aldoxime II also decomposed in alkali to give aldoxime II. This conversion provided a method of preparing aldoxime II, since the yield from direct condensation with hydroxylamine was too low to be satisfactory. It also showed that the two forms are stereoisomers rather than structural isomers. Comparison of the infra red spectra revealed that the peaks caused by the C=N vibrations were at

1605cm^{-1} and 1625cm^{-1} for forms I and II respectively. Kahovec and Kohlrausch (Monatsh., 1952, 83, 614) related the characteristic frequency of this linkage in the Raman spectrum of isomeric aldoximes to their configuration, finding that the one with the lower frequency was the α or cis form. Then LVI represents aldoxime I, the cis isomer, and LVII aldoxime II, the trans isomer. The values which these workers obtained for the benzaldoximes were 1635cm^{-1} and 1645cm^{-1}, while those for aliphatic aldoximes tended to be higher. The fact that the frequencies were lower in guaiazulene aldoximes than in typical benzenoid oximes may be attributed to the contributions from canonical forms LVI(b) and LVII(b) in which an electron pair from within the five-membered ring has migrated giving the nitrogen a negative charge. This would effectively lengthen the C=N linkage, changing the vibrational frequency and giving some of the free rotation associated with single bond character to the C=N bond.

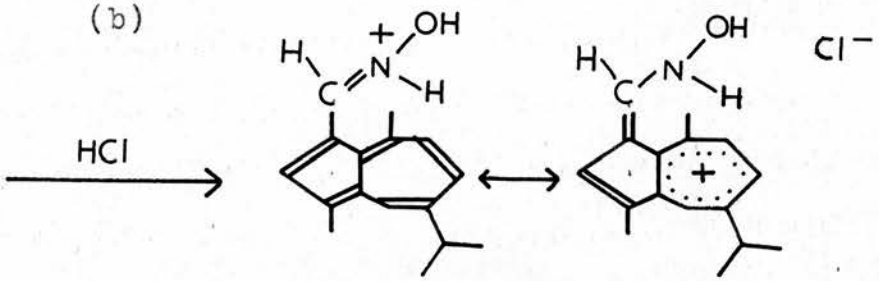
(a) LVI (b)

(a) LVII (b)

As the oximes are blue, the form (a) with conjugation throughout the molecule must be the most important of the two. The insolubility in alkali may be explained as follows in terms of forms bearing a negative, proton attracting, charge on the oxime group.



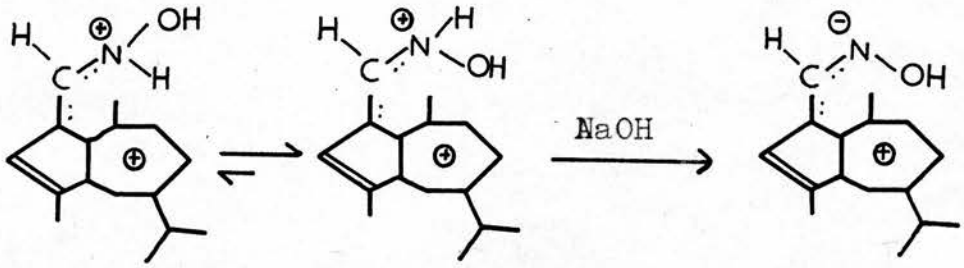
(a) LVI (b)



(a) LVIII (b)

The hydrochloride LVIII is red because there is no longer azulenic conjugation in the ring systems of the most important contributant, form LVIII(b). Hydrochloride formation follows a pattern analogous to that for the benzaldoximes. The lower melting α-benzaldoxime formed by condensation in alkali is less stable than the β-isomer. The hydrochloride of the former is only obtained below 0°C. and on recrystallisation it is

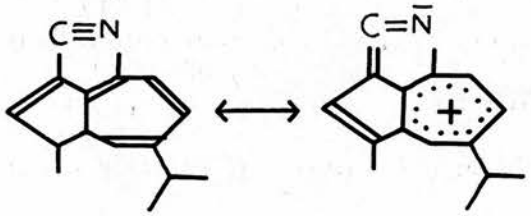
transformed to the β-hydrochloride. If hydrogen chloride is added at room temperature, this transformation is instantaneous. It appears that α-guaiazulene-aldoxime hydrochloride is a red compound which was converted very rapidly to the purple β-aldoxime hydrochloride. When the red α-oxime was treated with alkali, it was presumably converted during decomposition to the more stable β-configuration. This may be written as:



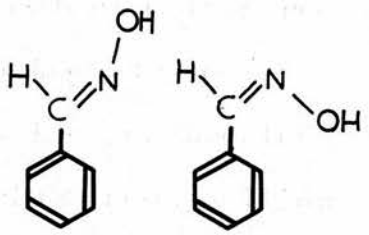
α form β form β form

Since it was thought that these basic oximes might quaternise readily to N-methyl-ethers (nitrones), α-guaiazulene-aldoxime was heated with methyl iodide. The molecule was in fact split giving a small quantity of guaiazulene, guaiazulene nitrile, LIX, and guaiazulene aldehyde, LV, along with unchanged oxime. The same products were obtained from the β-aldoxime. If both forms (a) and (b) of guaiazulene aldoximes, LVI and LVII, are important, then the compounds bear a partial negative charge on their nitrogen atom, whereas

normal oximes, e.g. benzaldoxime, LX (a) and (b), have positive charge on the oxygen atom.



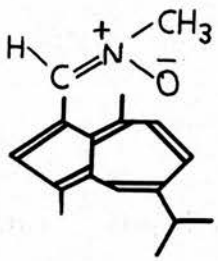
(a) LIX (b)



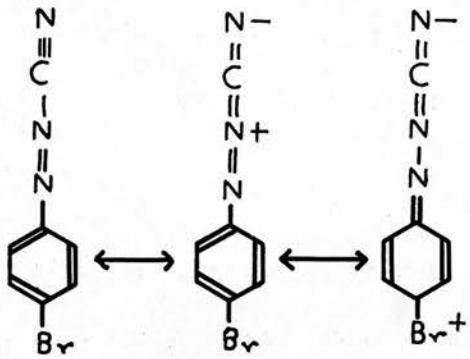
(a) LX (b)

Thus guaiazulene aldoximes show none of the normal acidity of oximes tending to lose a hydroxyl group rather than a proton. This process may occur during the reaction with methyl iodide. A methanol molecule would be formed, leaving a salt which need only lose a proton to form guaiazulene nitrile. An explanation of the formation of the aldehyde using the same reagent is more difficult to visualise. It may be that the nitrone, LXI, is formed and then completely hydrolysed to the carbonyl compound and methylhydroxylamine. Decomposition to guaiazulene appears to occur when the oximes are treated with any acidic reagent, for instead of hydrolysing to the aldehyde when heated with dilute hydrochloric acid, the oxime is converted exclusively to guaiazulene. Treatment of the α-guaiazulene-aldoxime with acetic anhydride in acid solution did not lead to acetylation of the hydroxyl group, but in fact to the formation of the nitrile. In a normal aldoxime this product would have been expected only

from the β-aldoxime acetate after reaction with sodium carbonate. Thus an aldoxime bearing negative charge on the nitrogen atom will readily dehydrate through loss of a hydroxyl group rather than acetylate through initial loss of a proton in the usual manner.



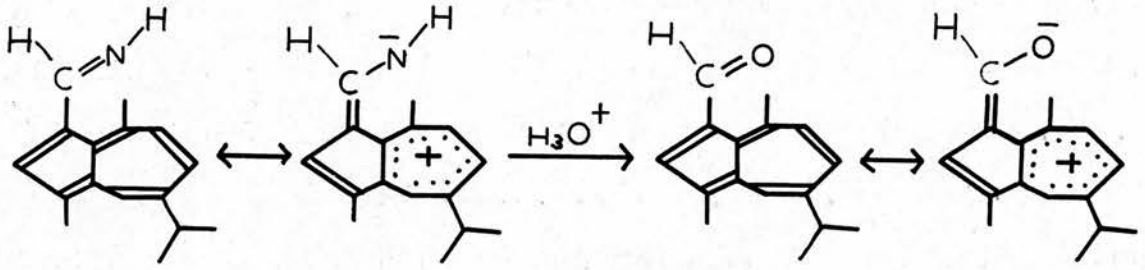
LXI



LXII

Guaiazulene nitrile showed obvious hypsochromic shifts with increase in polarity of the solvent due to the polarisability of the C≡N linkage. Proof of this abnormality is provided by the infra red spectrum. The vibrational frequency corresponding to this linkage is 2138 cm^{-1} which is equal to that of 4-bromo-benzene-diazocyanide, LXII, which contains a polarised C≡N group. (c.f. Sheppard and Sutherland. J.C.S., 1947, 453). Guaiazulene nitrile was not attacked by methyl magnesium iodide. The colour of the fraction which was proved by analysis to be guaiazulene aldehyde also varied with the solvent. It formed a 2:4-dinitro-phenylhydrazone of the same melting point as that prepared from the blue ether extract containing the products of the Gattermann reaction. Both the nitrile and the aldehyde were very soluble in all the common organic solvents tested. Their spectra are discussed at the end of the section.

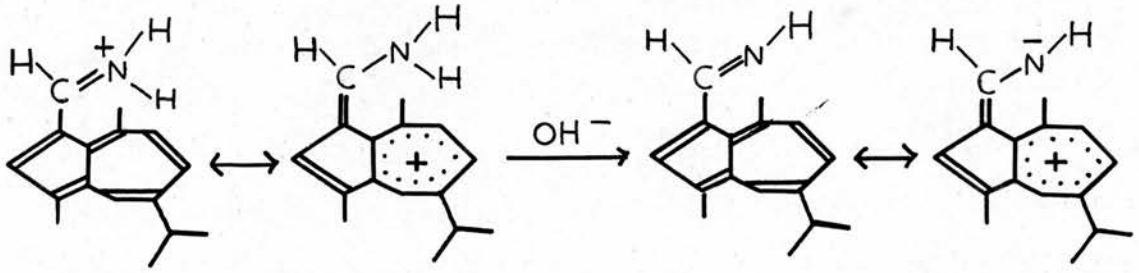
The violet colour of the aldehyde must be contrasted with the blue colour of the extract from the original Gattermann reaction. This was investigated using a second preparation. Before distilling off the ether from the blue extract it was diluted with high boiling petrol ether to overcome the difficulty of concentration in presence of excess peroxide. The solution was distilled to remove the ether but not the petrol ether. This was then chromatographed. A strongly adsorbed green band was observed at the top of the column and a violet band separated from which the aldehyde was obtained in 17% yield. The blue material which coloured the extract was probably the aldimine, LXIII, a precursor, of which only part was hydrolysed to the aldehyde in the original acid solution.



LXIII LV

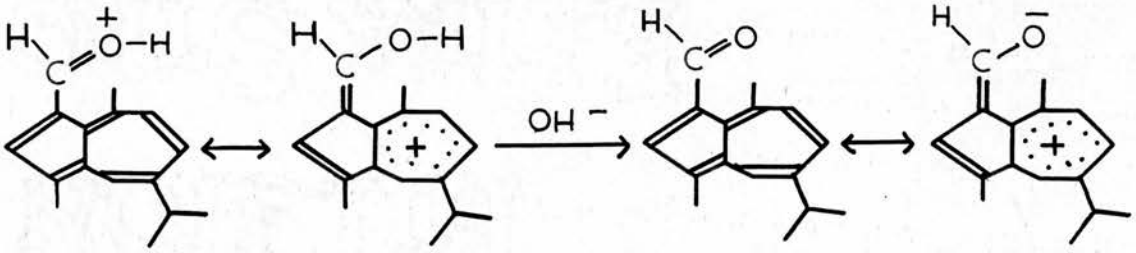
The aldimine extracted completely into ether together with some of the aldehyde, the remainder of which was extracted with a second portion of ether. The green band was probably due to decomposition of the aldimine.

The change in colour from red to blue when alkali was added to the initial mixture of products may be explained as:



(a) LXIV (b) (a) LXIII (b)

and



(a) LXV (b) (a) LV (b)

The hydrochloride of the aldimine has a greater contribution from LXIV (b) than from LXIV (a) with its three formal charges, whereas the free imine has predominant characteristics of the fully conjugated form, LXIII (a). The blue aldimine forms a red salt in acid and hydrolyses to a purple aldehyde of intermediate polarity. It seems reasonable to suppose that the aldehyde should have a greater contribution from form (b) than the aldimine, since the oxygen atom is more electro-negative than nitrogen.

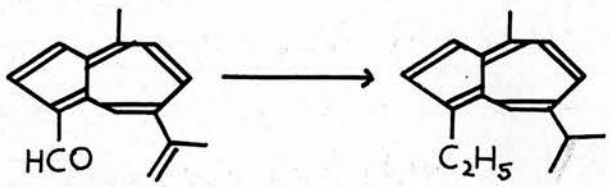
The yield of aldoximes prepared from the aldimine was 37% and that of the aldehyde isolated from the Gattermann reaction was only 17%. Therefore it must be assumed that the aldimine was converted to the oximes without formation of a carbonyl group as intermediate. The first maximum of the aldimine was 600-598mμ in ether solution and 417mμ in acid. When it was treated with phenyl magnesium bromide, and the products acidified, a green solution, red in transmitted light, was obtained, λmax.599 and 418mμ. The coloured material could not be extracted into petrol ether, benzene or ether, and it was irreversibly converted by alkali to a brown solution.

Rechromatography of the aldehyde caused part to decompose. It formed a rather unstable hydrochloride, LXV, which was shown by analysis to crystallise as a hydrate. The aldehyde formed a 2:4-dinitrophenylhydrazone and oximes identical with those prepared from the aldimine. It could not be oxidised with moist silver oxide.

Guaiazulene-3-aldehyde may be compared with lactaroviolin, a naturally occurring azulenic aldehyde isolated by Willstaed from Lactarius deliciosus (Ber., 1935, 68B, 333). Plattner and Heilbronner (Exper., 1945, 1, 233) showed that the colour of lactaroviolin changed from purple to blue on partial hydrogenation. Complete hydrogenation by Karrer, Ruckstuhl and Zbinden (Helv. Chim. Acta, 1945, 28, 1176) yielded a primary alcohol $C_{15}H_{27}OH$,

and a hydrocarbon, $C_{15}H_{28}$, by loss of oxygen. It was also proved, by using the Wolff-Kishner reaction, that the carbon skeleton was identical with that of lactarazulene, a naturally occurring trialkyl substituted azulene. (This was later shown to be 1:4-dimethyl-7-isopropenyl-azulene by hydrogenation to guaiazulene.) Consequently these workers pointed out that there were three possible structures for lactaroviolin, one with the aldehyde group on the isopropenyl side chain, and the others with it on positions-1 or -4. The first structure was ruled out by Sorm, Benesova and Herout (Chem.Listy, 1953, 47, 1856) who obtained evidence by ozonisation of the presence of a methylene group in lactaroviolin. The 1-aldehyde structure was favoured by Plattner, Heilbronner, Schmid, Sandrin and Fürst (Chem.and Ind.,1954, 1202) since they did not expect a 4-aldehyde to show such a large hypsochromic shift from that of guaiazulene. This argument was extended by Heilbronner and Schmid (Helv.Chim.Acta, 1954, 37, 2018) who agreed with Galloway, Reid and Stafford(Chem.and Ind., 1954, 724) that the hypsochromic effect of changing to solvents which hydrogen bond with the carbonyl group is an indication of increased localisation on the oxygen atom of an electron from the negatively charged five-membered ring. The basic nature of the molecule was explained by Heilbronner and Schmid as addition of a proton to the oxygen atom and not to form the azulenium ion, since the infra red

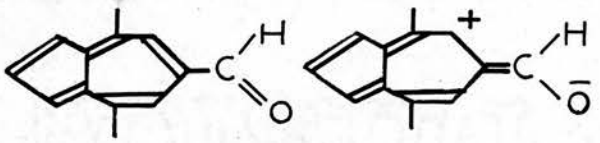
spectrum showed the presence of a hydroxyl group. The ultra violet spectra in neutral and acid solution are essentially the same. This was considered to be due to the polar nature of the carbonyl group even in a non-polar environment, as in tropone and tropolone and is supported by the low carbonyl vibrational frequency of lactaroviolin which is 1658cm^{-1}, 23cm^{-1} lower than that of other aromatic aldehydes. Finally Sorm and co-workers (Coll.Czechoslov.Chem.Commun., 1955,20,227) converted lactaroviolin to an ethyl-methyl-isopropyl-azulene by reaction with methyl magnesium iodide followed by dehydration and hydrogenation of the product. This was identical with 1-ethyl-4-methyl-7-isopropyl-azulene, and thus lactaroviolin, LXVI, has the aldehydic group on position-1.



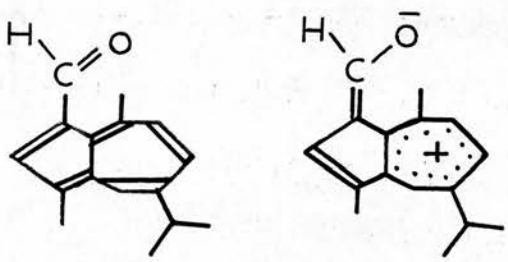
LXVI

The properties of synthetic guaiazulene-3-aldehyde and the naturally occurring 1-aldehyde are thus very similar. They differ in colour from 4:8-dimethyl-azulene-6-aldehyde prepared by Arnold (Ber., 1954, 87, 257) which is pure blue. The position of

the maximum of 4:8-dimethyl-azulene is about 560 mμ (purple). Therefore a bathochromic shift roughly equivalent to that found on introducing a 6-carbethoxy group in azulene has been produced by this 6-aldehyde group. There is no possibility of an electron from the negatively charged five-membered ring being localised on the oxygen atom, the cause of a hypsochromic shift in a 1-aldehyde. The normal electromeric influence of a carbonyl group is all that can occur. It may be pictured as LXVII (b) as compared with LV (b).



(a) LXVII (b)

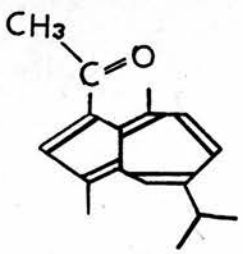


(a) LV (b)

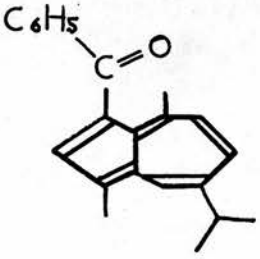
The infra red spectrum of the 6-aldehyde shows a vibrational frequency of 1705cm^{-1} which is that of a normal aromatic aldehyde whereas lactaroviolin and guaiazulene-3-aldehyde show values of 1658cm^{-1} and 1638cm^{-1} respectively. The difference of 20cm^{-1} may be due to the presence of some water in the sample of guaiazulene aldehyde, but each has a drop in frequency of at least 50cm^{-1} due to the unusual partly polarised nature of the aldehyde group.

An exploration of routes to other acyl derivatives of guaiazulene was the next project. Anderson, Nelson and Tazuma (J.A.C.S. 1950, 72, 3824; J.A.C.S. 1953, 75, 4980) have prepared di- and monoacetyl azulene using acetic anhydride and aluminium chloride and stannous chloride respectively as catalyst. As an alternative, a Hoeben-Hoesch reaction was attempted using acetonitrile and zinc chloride in the presence of dry ether saturated with hydrogen chloride, and in a second experiment methylene dichloride as solvent and aluminium chloride as catalyst, but no azulenic material other than returned guaiazulene was obtained in either case.

Since guaiazulene appeared to have a carbanionic structure, it was thought that it might have the property shown by methine enol betaines (e.g. XXXII, p.48) of reacting with acyl halides or acetic anhydride without use of a catalyst (Krönhke. Ber., 1935, 68, 1177; Ber., 1937, 70, 1114). Acetyl bromide was found to react at room temperature with guaiazulene giving acetyl guaiazulene, LXVIII, in 37% yield. Using benzoyl bromide, it was found necessary to boil the reaction mixture in petrol ether (80-100°C.) to obtain even an 8% yield of benzoyl guaiazulene, LXIX. This was increased to 13% if no solvent was used and the reactants heated for 10 minutes in a boiling water bath.



LXVIII



LXIX

A second product of this acetylation, a green material, decomposed on rechromatography to a mixture of yellow compounds. It formed a picrate and also a purple T.N.B. complex (yellow mother liquors) which was decomposed to a blue/green hydrocarbon by addition of acetone. As an alternative method of purification, the T.N.B. complex was reduced with stannous chloride in a mixture of glacial acetic acid and concentrated hydrochloric acid, and the resulting blue material distilled at 60°C. The spectrum of the distillate, which did not crystallise, was found to be identical with that of guaiazulene. X-ray powder photographs of the T.N.B. complex and guaiazulene T.N.B. complex did not appear to be identical, but polymorphism is known to be a property of azulene T.N.B. complexes. Since the green fraction was the only one eluted from the column by petrol ether, it seems probable that it was in fact guaiazulene together with a yellow material of the same polarity and therefore not separable from it by this means.

In an experiment using the method of acetylation of Anderson, Nelson and Tazuma (acetic anhydride with stannic chloride), a similar green fraction was obtained together with a 42% yield of acetyl guaiazulene. This may be compared with the work of Ukito, Watanabe and Miyasaki (J.A.C.S. 1954, 76, 4584) who prepared acetyl guaiazulene in 18% yield by the reaction of acetic anhydride or acetyl chloride with guaiazulene in the

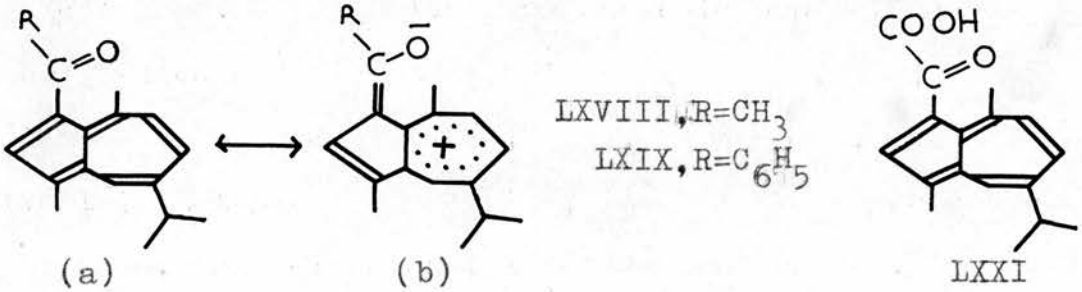
presence of aluminium chloride. They made no mention of a green hydrocarbon fraction. A low yield, 10%, of benzoyl guaiazulene was obtained when benzoyl chloride was reacted with guaiazulene using aluminium chloride as catalyst. A better method of preparation is described in section B of this thesis.

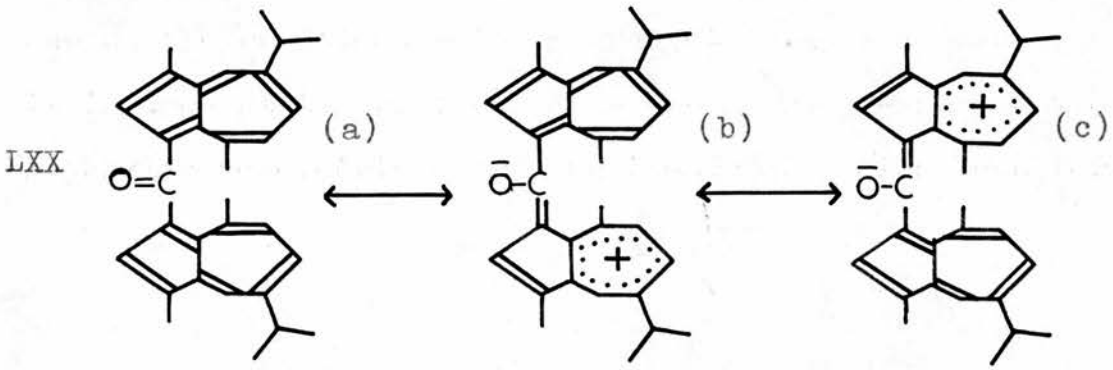
Comparable yields of the acyl derivatives are thus afforded in the experiments carried out in the absence of a catalyst. Galloway, Reid and Stafford (Chem. and Ind., 1954, 724) have pointed out that this may throw light on the action of catalysts in the Friedel Crafts reaction, since azulenes are partly polarised, and lie in an intermediate position between benzenoid hydrocarbons which require a catalyst for acylation and the fully polarised salts, e.g. sodium ethylacetoacetate which do not.

Oxalyl chloride also reacts with guaiazulene in the absence of a catalyst, but it gives two azulenic products. If petrol ether is used as solvent, diguaiazulyl ketone, LXX, and guaiazulene-3-glyoxylic acid, LXXI, are formed. But when the solvent is methylene dichloride, in which the reaction complex is soluble, only diguaiazulyl ketone was present. A small acidic fraction isomeric with the glyoxylic acid was found in one of the reactions using petrol ether. From the spectrum, it is thought to be 2:4-dimethyl-7-isopropyl-azulene-1-or-3-glyoxylic acid, derived from an isomer of guaiazulene formed

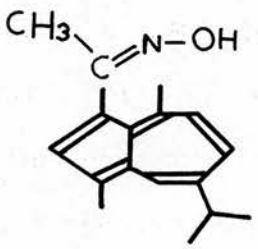
during dehydrogenation of the sesquiterpene oils and present as an impurity in the starting material.

The infra red spectra of acetyl guaiazulene, benzoyl guaiazulene and diguaiazulyl ketone show carbonyl vibrational frequencies of 1674 and 1638, 1634 and 1616cm^{-1} respectively in carbon tetrachloride as solvent. These may be compared with values of about 1690, 1660, 1640 and 1630cm^{-1} for acetophenone, benzophenone, and tropone and tropolone respectively. Thus the three guaiazulyl ketones have the carbonyl group partially polarised as in guaiazulene aldehyde and tropone and tropolone. Acetyl guaiazulene and benzoyl guaiazulene have two main contributing forms LXVIII (a) and (b) and LXIX (a) and (b), but diguaiazulyl ketone with lowest C=O frequency has the possibility of contribution from a third form, and is a hybrid of LXX (a), (b) and (c). Details of the infra red spectra are given together with the absorption spectra at the end of the section.

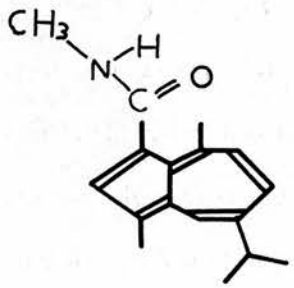




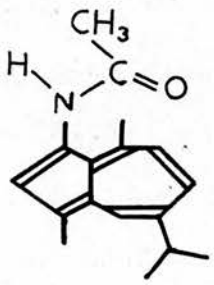
Acetyl guaiazulene formed a 2:4-dinitrophenylhydrazone and a T.N.B. complex. The analysis of the former shows the nitrogen content to be lower than the calculated value. When boiled in pyridine solution with hydroxylamine hydrochloride, acetyl guaiazulene gave only one oxime in 42% yield. The infra red spectrum of this acetoxime had the C=N vibrational frequency at 1629cm^{-1} which is very close to that of β-guaiazulene-aldoxime. But the value for the carbonyl group in acetyl guaiazulene is higher than that of guaiazulene aldehyde, therefore it may be supposed that this is the guaiazulene acetoxime of lower C=N frequency and is probably the α-isomer. Certainly azulene acetoxime prepared by Anderson and co-workers (J.A.C.S. 1953, 75, 4980) underwent a Beckmann rearrangement to N-acetyl-azulamine which would normally only occur with the α isomer. The blue guaiazulene acetoxime, LXXII, was basic, forming a red hydrochloride in presence of hydrogen chloride. The explanation for this is the same as for the aldoxime hydrochlorides.



LXXII



LXXIII

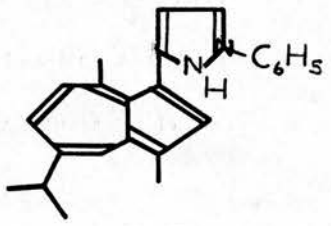


LXXIV

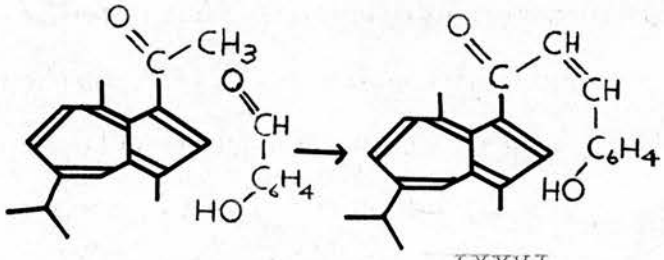
But the reaction with methyl iodide was different from that of the guaiazulene aldoximes. The products were three unstable blue fractions which became yellow or orange in acid solution. There was a smell of methylamine which suggests that a reaction similar to the Beckmann rearrangement had occurred. Since methyl iodide brought about the dehydration of α-guaiazulene-aldoxime, the normal specificity of nitrile formation to the β-isomer does not appear to apply. It seems probable, then, that the one isomer of guaiazulene acetoxime would rearrange in both cis and trans manner to guaiazulene-3-carboxylic acid methyl amide (red), LXXIII, and N-acetyl-3-amino-guaiazulene, LXXIV. The azulene analogues of the hydrolysis products, 3-amino-azulene and azulene-3-carboxylic acid (red) have both been shown to be too unstable for isolation by Anderson and co-workers. If one of the blue fractions was N-acetyl-guaiazulyl-amine it did not have the stability of its azulene analogue. The tendency of the guaiazulene aldoximes to decompose in acid media through initial loss of the hydroxyl group is also present in the acetoxime which is converted to guaiazulene in presence of trichloracetic acid.

Acetyl guaiazulene when warmed with phenylhydrazine in an ethanolic solution containing glacial acetic acid gave a blue/green compound which would not crystallise. It had a good analysis for the carbon and nitrogen content of the phenylhydrazone

but the hydrogen was only about 52% of the calculated value. A red methiodide was prepared from it and this was treated with picric acid. The result was a brown amorphous solid of very indefinite melting point which was probably a mixture. Condensation of acetyl guaiazulene with ethyl formate yielded a green solution which was treated with an ethanolic solution of phenylhydrazine. The resulting green solution, red in transmitted light, did not crystallise. It was heated with methyl iodide, giving an orange/red compound which, since it did not crystallise, was treated with picric acid. The analysis of the product showed that it was not the expected metho-picrate of 1-phenyl-3-guaiazulyl-pyrazole, LXXV. The series of attempts to condense acetyl guaiazulene to form analogues of chalcones of the type LXXVI were inconclusive.



LXXV

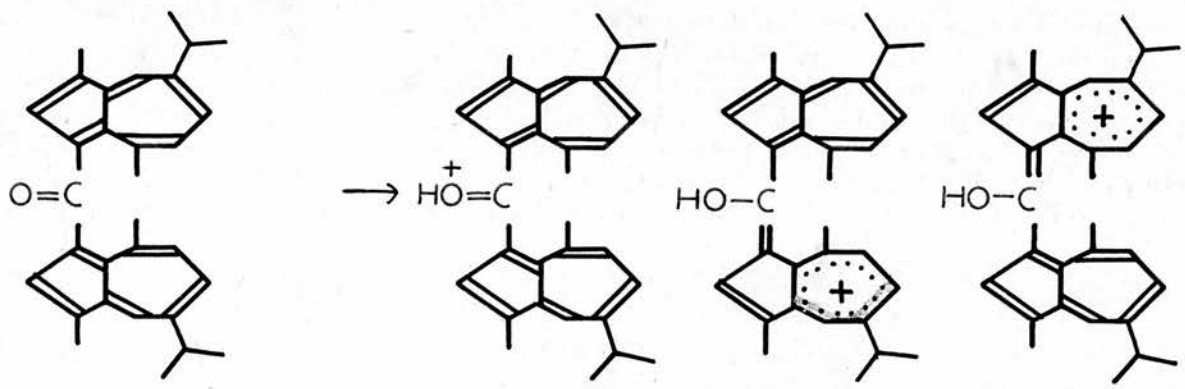


LXXVI

Application of Anderson and co-workers' method of hypoiodite oxidation (J.A.C.S. 1953, 75, 4980) left acetyl guaiazulene unchanged. In addition, Zimmermann's method (Thesis; Eidg. Techn. Hochschule, Zurich, 1953) for applying the Grignard reaction to acetyl guaiazulene, although successful in repetition

of his work, (also reported by Ukito, Watanabe and Miyasaki (J.A.C.S. 1954, 76, 4584)) gave only non-azulenic orange products with benzyl magnesium bromide. The same result was obtained together with some guaiazulene from reactions with phenyl magnesium bromide on acetyl guaiazulene and methyl magnesium bromide on benzoyl guaiazulene. Less violent conditions for Grignard reactions were employed by Sorm and co-workers (Coll. Czechoslov.Chem.Commun., 1955, 20, 227) for use with lactaroviolin. No products other than guaiazulene and unchanged starting material were obtained by boiling diguaiazulyl ketone in dry ether with a very large excess of methyl magnesium iodide. Neither benzoyl guaiazulene or diguaiazulyl ketone formed 2:4-dinitrophenylhydrazones or T.N.B. complexes. This progressive lack of reactivity is reflected in the decreasing carbonyl vibrational frequencies of acetyl and benzoyl guaiazulene and diguaiazulyl ketone.

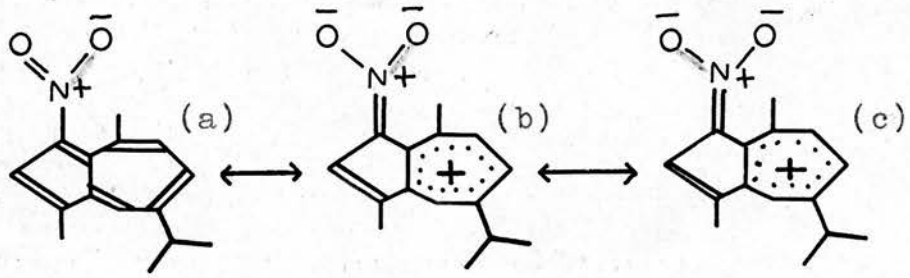
The hydrochloride of diguaiazulyl ketone differs from those of guaiazulene aldehyde, aldoximes and acetoxime in being the colour of permanganate. This is explained by the presence of two guaiazulyl groups, in only one of which electron localisation occurs when a proton is added.



When the Clemmensen reduction was applied to benzoyl guaiazulene only non-azulenic products were obtained, but using lithium aluminium hydride two separate blue/green materials were isolated in reactions under different conditions. Neither crystallised and the yields were too low for the materials to be investigated other than spectrographically. One, eluted in ether had λmax. in the same place as guaiazulene, but the other, which was eluted with petrol ether (i.e. a hydrocarbon), had a bathochromic shift of about 20m μ which would be expected if a benzyl group was present in position-3. The product which was obtained together with unchanged guaiazulene from the reaction of guaiazulene with benzyl chloride using aluminium chloride or stannic chloride as catalyst had the absorption maximum in the same position. It crystallised, but the analysis agreed with either that of benzyl guaiazulene or diguaizulyl ethane. Anderson and co-workers (J.A.C.S. 1955, 77, 6321) report the formation of benzyl azulene in 5.6% yield using the same reagents with azulene.

Guaiazulene was nitrated to compare the effect of this electron attracting group with that of a carbonyl substituent. Tetranitromethane was employed and it was found that when 0.6 moles were used only nitro-guaiazulene, LXXVII, was obtained, but with 0.3 moles, guaiazulene, nitro-guaiazulene and guaiazulene aldehyde (in very small amount) were present. Nitro-azulene was prepared from azulene by Anderson, Nelson and Tazuma

(J.A.C.S. 1953, 75, 4980) using cupric nitrate and acetic anhydride, and by Treibs (Angew.Chem. 1955, 67, 76) using urea nitrate or nitric acid free from nitrous acid. A hypsochromic shift on introduction of the nitro group was reported, and the fact that the absorption spectrum both in the ultra violet and visible region was different from that of all azulenes previously investigated. The infra red spectrum of nitro-guaiazulene showed the $C\text{-}NO_2$ vibrational frequency to be 1526 and 1230cm^{-1}. Bellamy (The Infra-red Spectra of Complex Molecules. Methuen, London. 1954) gives the values for aromatic nitro compounds as 1560-1500 and 1350-1300cm^{-1}, with values reduced to 1515cm^{-1} by introduction of an electro-negative group in the para position of the benzene ring. This is evidence of the existence of contributions from forms LXXVII (b) and (c) which have electron localisation on the oxygen atoms.



LXXVII

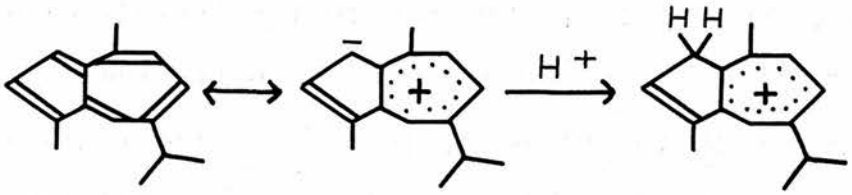
Reduction of nitro-guaiazulene with lithium aluminium hydride or zinc dust and alkali decomposed the molecule to non-azulenic products. Attempts by Anderson and co-workers

(J.A.C.S. 1953, 75, 4980) led to the same result, and Treibs and Ziegenbein (Ann., 1954, 586, 194) regard the isolation of amino azulene as impossible due to its extreme instability to light and air. Reductive acetylation, however, by Anderson and co-workers (J.A.C.S. 1953, 75, 4980) gave crystalline N-acetyl-azulamine. This was also obtained by use of the Beckmann rearrangement on azulene acetoxime as mentioned earlier in the discussion of the reactions of guaiazulene acetoxime. In contrast to nitro-guaiazulene which has contributions from polar forms, LXXVII (b) and (c) due to the electron attracting property of the nitro group, an amino group would tend to donate electrons to the already negatively charged five-membered ring and thus induce instability.

Absorption spectra.

Fig.1 shows the spectrum of guaiazulene in hexane, in methylene dichloride saturated with hydrogen chloride and in methylene dichloride saturated with T.N.B. The curve representing the spectrum in neutral solution may be regarded as consisting of three parts, a broad band in the 500-720mμ region which is responsible for the blue colour, two peaks close together at about 340-370mμ and two others below 300mμ. The spectrum in acid solution, on the other hand, shows no absorption in the visible region, a higher peak at 340mμ and little change in the ultra violet. The broad longest wavelength band in guaiazulene may be considered as the 'azulenic' or 'betaine' band due to the peculiar energy state of the resonance hybrid to which nineteen canonical forms contribute. The lack of this band and rise of the second peak when in acid solution is an expression of the change in the molecule to the guaiazulenium cation, LIV, by addition of a proton. A summary of the first discussion of this salt formation by Plattner, Heilbronner and Weber (Helv.Chim.Acta, 1952, 35, 1036) and Heilbronner and Simonetta (Helv.Chim.Acta, 1952, 35, 1049) is on pp.16 and 17. The close analogy between the absorption in the ultra violet for both the 'betaine' and the cation suggests that similar excitations are responsible

and this requires contributions to the resonance hybrid of forms in which there is electron localisation on carbon atom one. This occurs partially in the neutral molecule and more completely in the ion, where the electrons on carbon atom one are shared with the added proton.



III LIV

A hypsochromic shift and higher absorption in the first band is found when the solution is saturated with T.N.B. due to the induced polarisation by the complexed nitro groups. The spectrum in the ultra violet region could not be examined below 420mμ because of the strong absorption in the ultra violet by the nitro compound.

The positions and log E values of the absorption maxima of the compounds whose preparation and properties have been described are as follows:

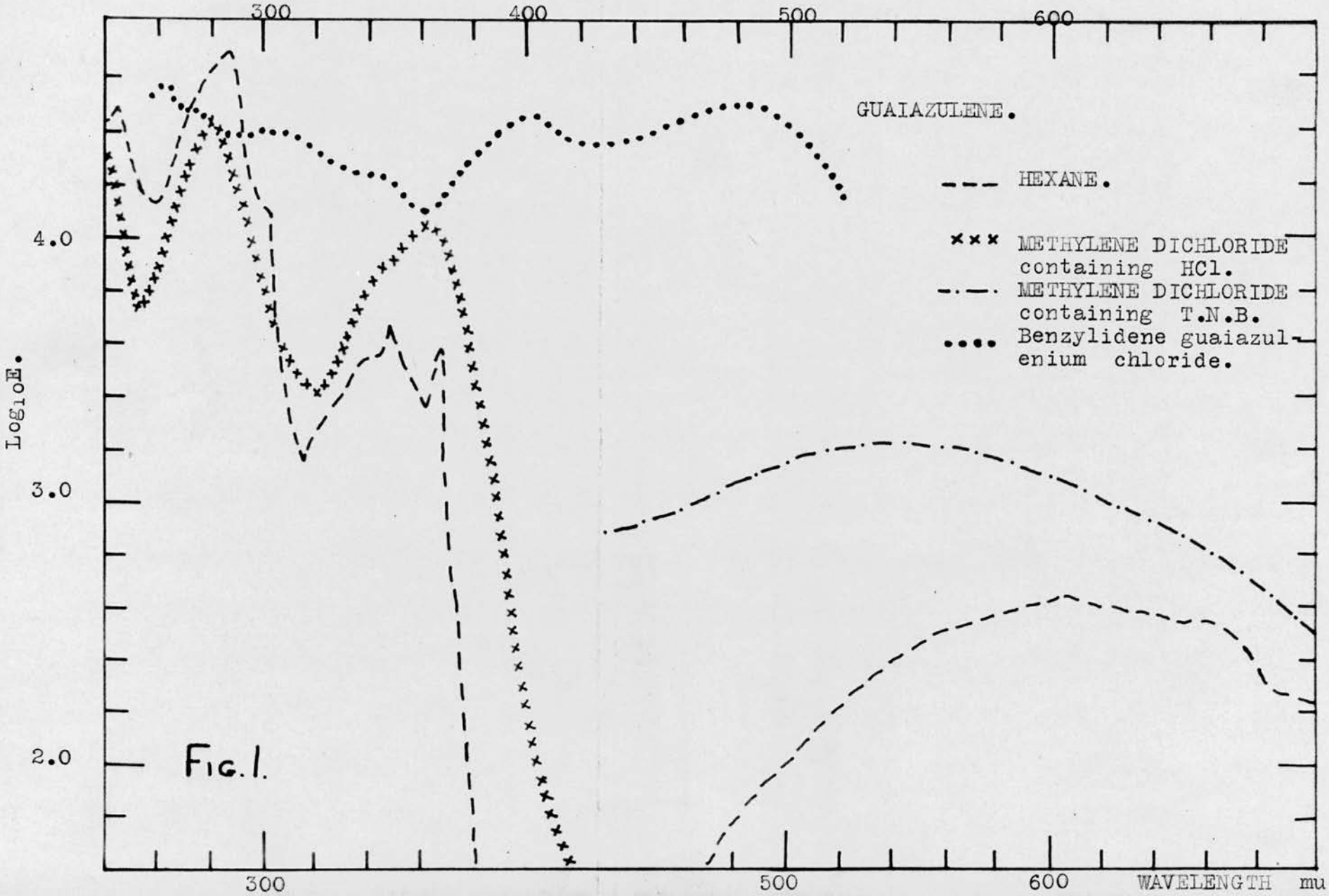

300
400
500
600
GUAIAZULENE.
HEXANE.
METHYLENE DICHLORIDE containing HCl.
METHYLENE DICHLORIDE containing T.N.B.
Benzylidene guaiazulenium chloride.
4.0
3.0
2.0
Log10E.
300
500
600
WAVELENGTH mu.

Fig. 1.

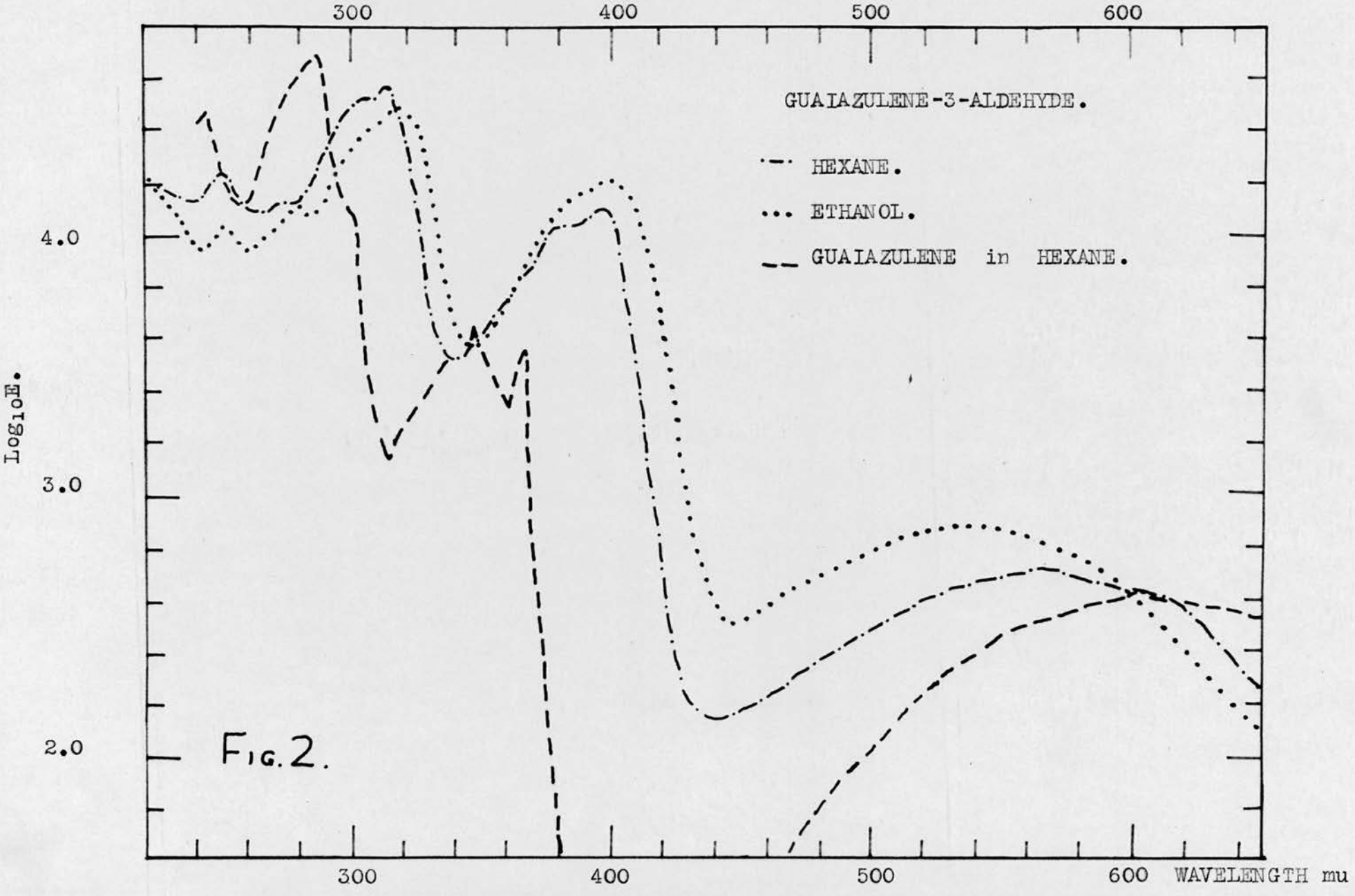

300
400
500
600
GUAIAZULENE-3-ALDEHYDE.
HEXANE.
ETHANOL.
GUAIAZULENE in HEXANE.
4.0
3.0
2.0
Log10E.
300
400
500
600
WAVELENGTH mu

FIG. 2.

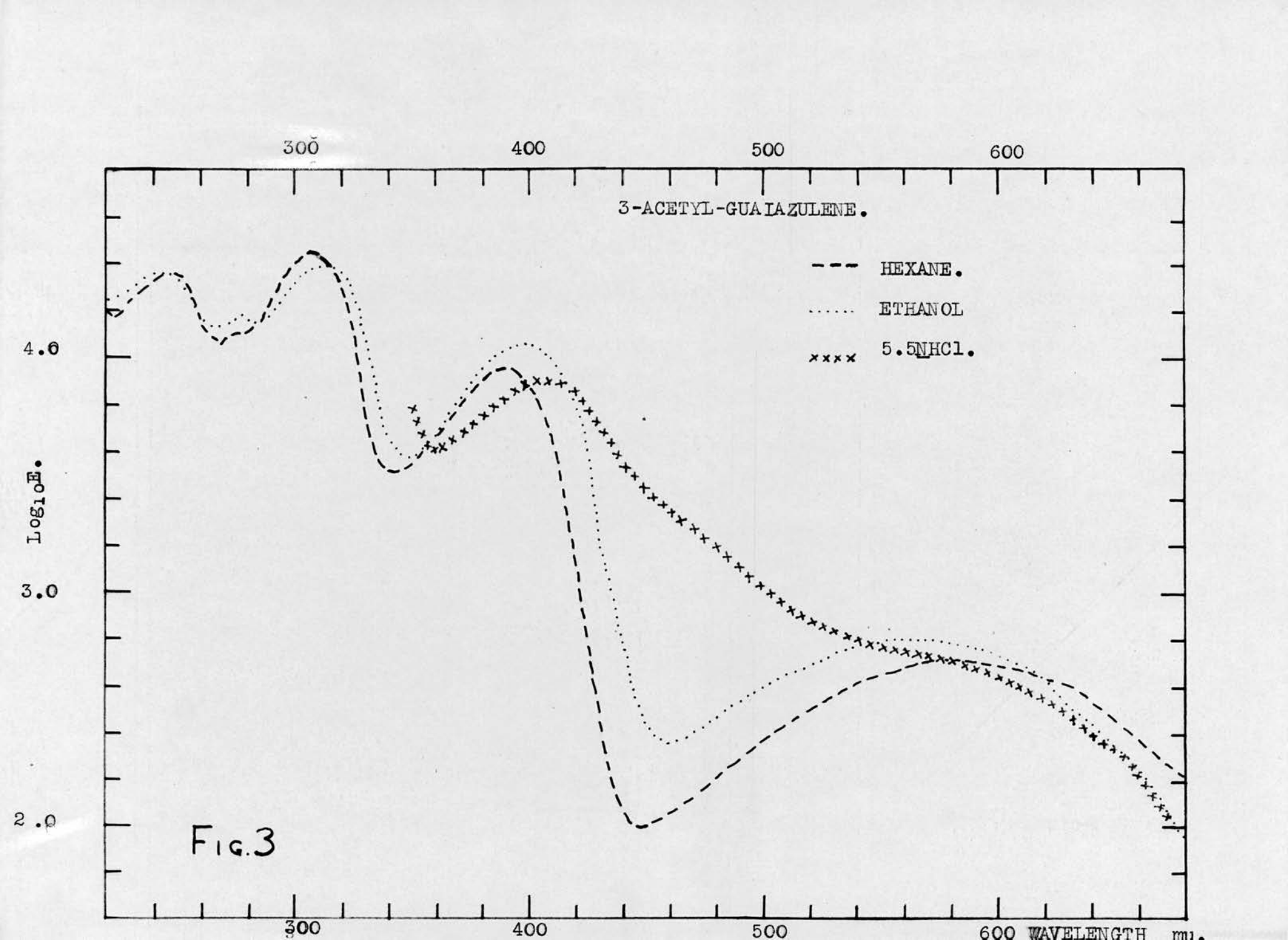

300
400
500
600
3-ACETYL-GUAIAZULENE.
HEXANE.
ETHANOL
5.5NHCl.
4.0
3.0
2.0
Log10E.
300
400
500
600 WAVELENGTH mμ.

FIG. 3

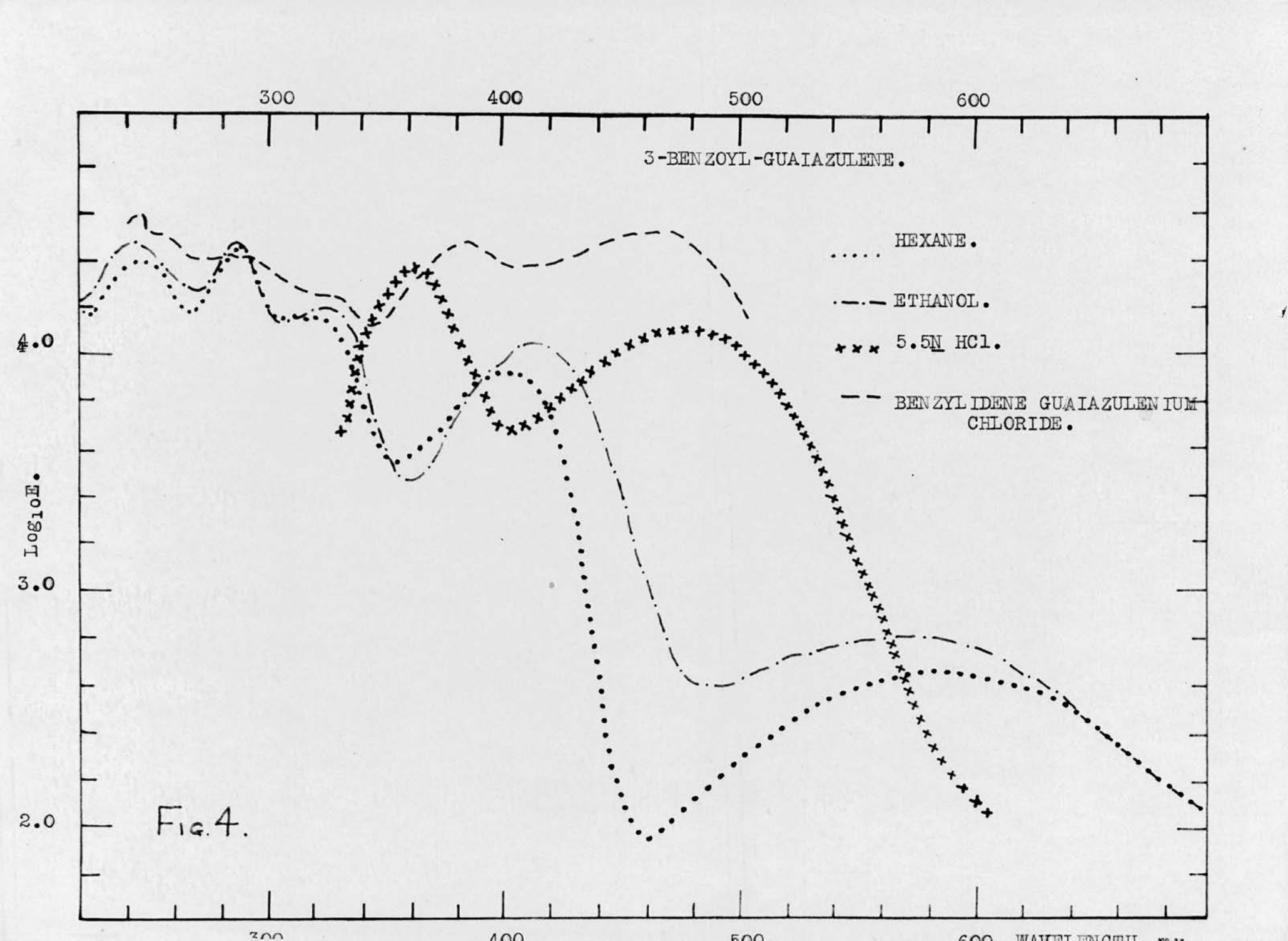

300
400
500
600
3-BENZOYL-GUAIAZULENE.
HEXANE.
ETHANOL.
5.5N HCl.
BENZYLIDENE GUAIAZULENIUM CHLORIDE.
4.0
3.0
2.0
Log10E.
WAVELENGTH mμ

Fig. 4.

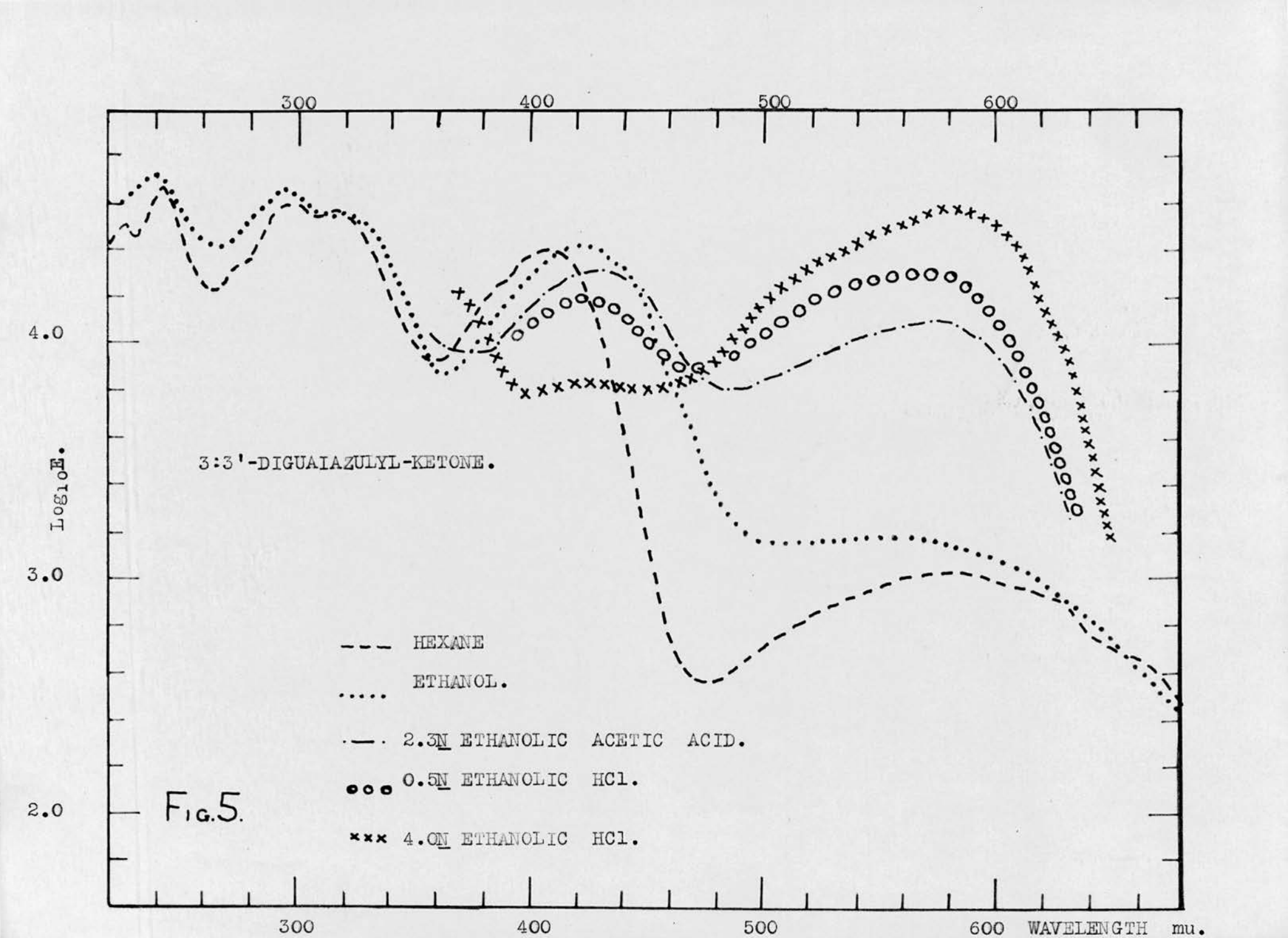

300
400
500
600
4.0
3.0
2.0
Log10E.
3:3'-DIGUAIAZULYL-KETONE.
HEXANE
ETHANOL.
2.3N ETHANOLIC ACETIC ACID.
0.5N ETHANOLIC HCl.
4.0N ETHANOLIC HCl.
300
400
500
600 WAVELENGTH mu.

FIG. 5.

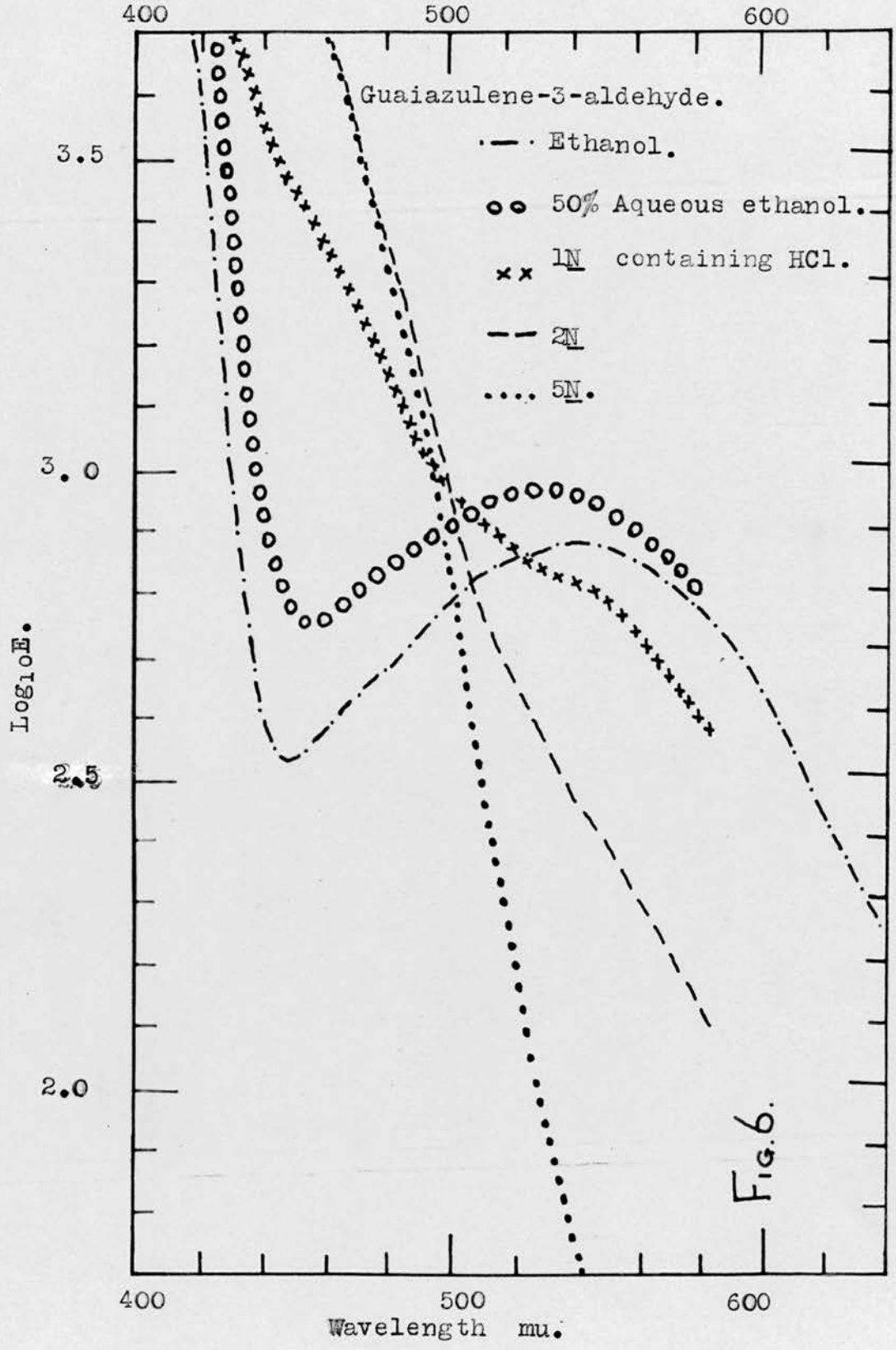

Guaiazulene-3-aldehyde.
Ethanol.
50% Aqueous ethanol.
1N containing HCl.
2N
5N.
Log10E.
3.5
3.0
2.5
2.0
400
500
600
Wavelength mu.

Fig. 6.

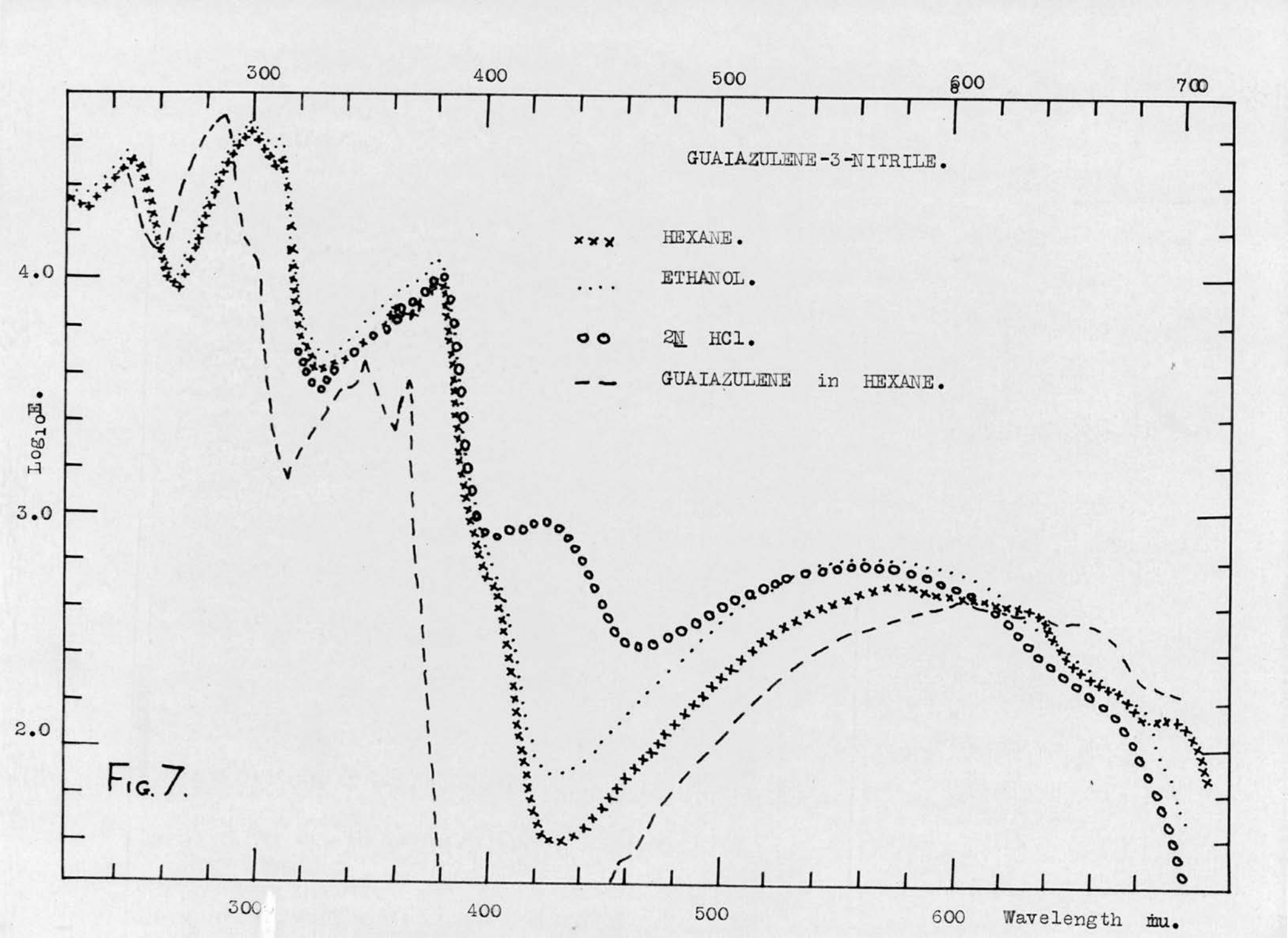

GUAIAZULENE-3-NITRILE.
HEXANE.
ETHANOL.
2N HCl.
GUAIAZULENE in HEXANE.
Log10E.
4.0
3.0
2.0
300
400
500
600
700
Wavelength mu.

FIG. 7.

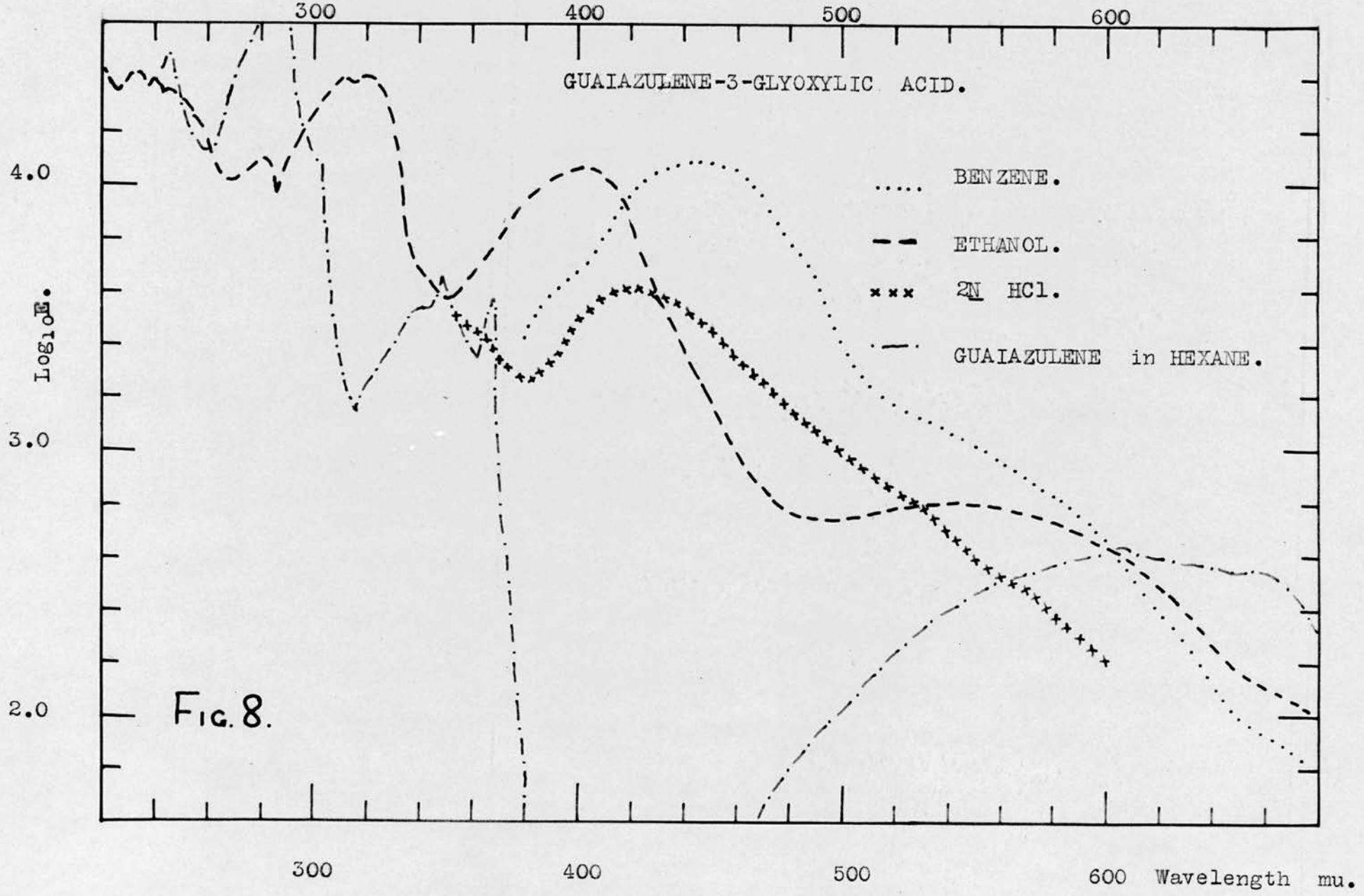

300
400
500
600
GUAIAZULENE-3-GLYOXYLIC ACID.
BENZENE.
ETHANOL.
2N HCl.
GUAIAZULENE in HEXANE.
4.0
3.0
2.0
Log10E.
300
400
500
600 Wavelength mu.

Fig. 8.

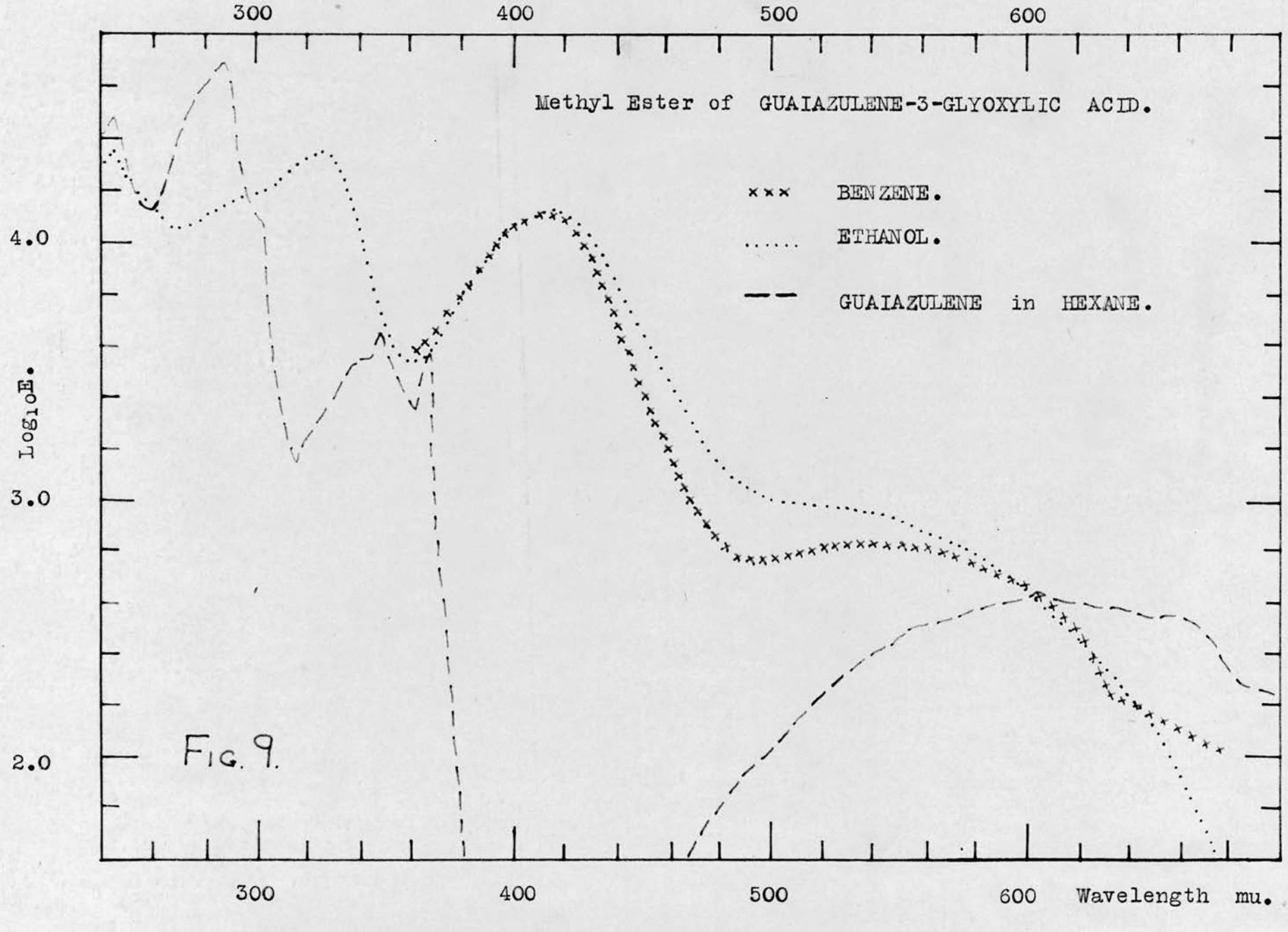

300
400
500
600
Methyl Ester of GUAIAZULENE-3-GLYOXYLIC ACID.
BENZENE.
ETHANOL.
GUAIAZULENE in HEXANE.
4.0
3.0
2.0
Log10E.
300
400
500
600
Wavelength mu.

Fig. 9.

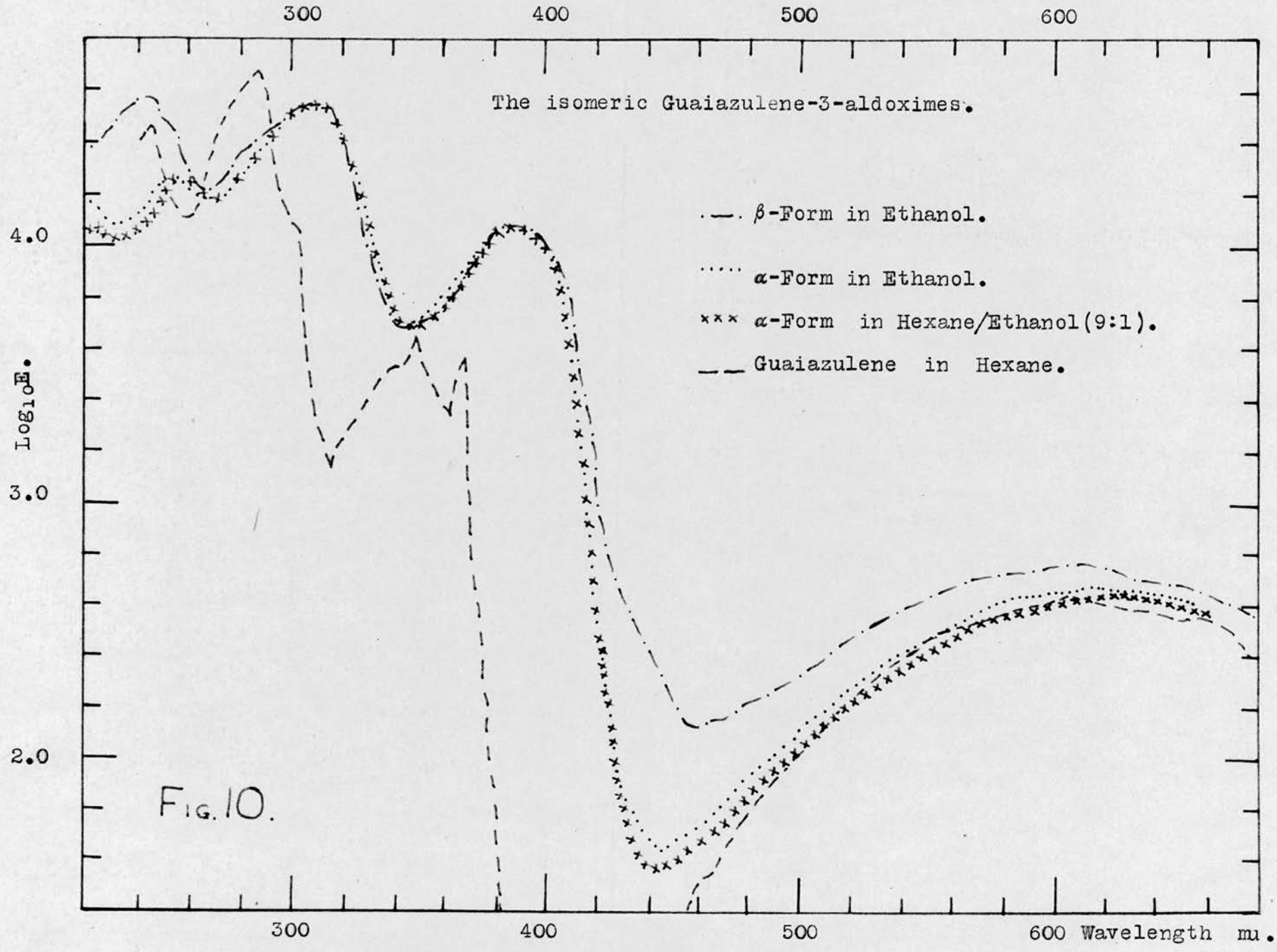

300
400
500
600
The isomeric Guaiazulene-3-aldoxime.
β-Form in Ethanol.
α-Form in Ethanol.
α-Form in Hexane/Ethanol(9:1).
Guaiazulene in Hexane.
4.0
3.0
2.0
Log10E.
300
400
500
600 Wavelength mμ.

FIG. 10.

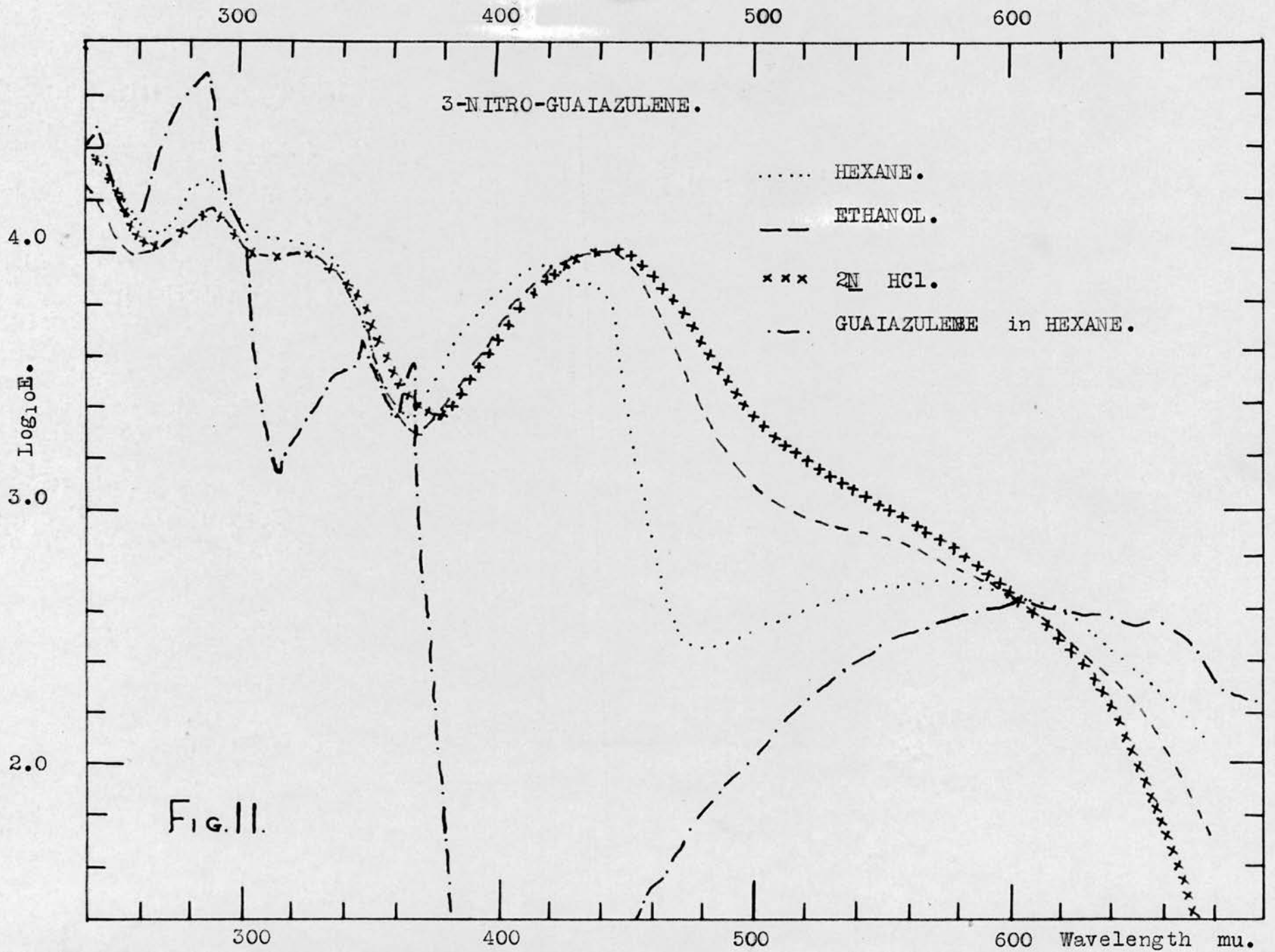

300
400
500
600
3-NITRO-GUAIAZULENE.
..... HEXANE.
— — ETHANOL.
××× 2N HCl.
.—. GUAIAZULENE in HEXANE.
4.0
3.0
2.0
Log10E.
300
400
500
600 Wavelength mu.

Fig. 11.

Guaiazulene:- (fig.1)	λ max.	$Log_{10}E_{Molar}$
in hexane	605mμ	log E 2.64
	367	3.58
	350	3.70
	285	4.67
	246	4.46
in methylene dichloride	---	----
saturated with HCl	360mμ	log E 4.04
	280	4.43
in methylene dichloride	538mμ	log E 3.21
saturated with T.N.B.	---	----

Guaiazulene-3-aldehyde:- (fig.2)		
in hexane	568mμ	log E 2.73
	397	4.09
	314	4.56
	276	4.13
	250	4.23
in ethanol	538mμ	log E 2.88
	401	4.20
	318	4.48
	278-80	4.10
	251-2	4.03
	238	3.98

in 50% aqueous ethanol, the first maximum was at 526-30mμ, $log_{10}E$,2.96 (fig.6). The same diagram shows the absorption curves of the aldehyde in ethanol solution containing 50% of N, 2N and 5N aqueous hydrochloric acid. They have no maximum in the region above 400mμ.

Acetyl guaiazulene:- (fig3)

	λmax.	$Log_{10}E_{Molar}$
in hexane	580mμ	log E 2.72
	389-90	3.96
	306	4.45
	249	4.36
in ethanol	558-62mμ	log E 2.80
	396-7	4.06
	311	4.39
	277-78	4.17
	238-41	4.36
in 2N ethanolic HCl	408mμ	log E 3.92
	---	----

Benzoyl guaiazulene:- (fig.4)

in hexane	582-4mμ	log E 2.66
	399	3.93
	320-21	4.16
	307-8	4.16
	289	4.46
	249	4.39
in ethanol	564-68mμ	log E 2.78
	413	4.03
	325	4.18
	289	4.46
	240	4.46
in 9.7N ethanolic HCl	470-80mμ	log E 4.08
	360	4.36
	---	----

Diguaiazulyl ketone:- (fig.5)

	λ max.	Log_{10} E Molar
in hexane	582mμ	log E 3.02
	407	4.38
	316	4.56
	296-300	4.59
	242	4.64
in ethanol	550mμ	log E 3.18
	424	4.42
	313	4.56
	297	4.66
	240	4.72
in 2.3N ethanolic glacial acetic acid	568mμ	log E 4.10
	427	4.32
	---	----
in 0.05N ethanolic HCl	566mμ	log E 4.32
	422	4.22
	---	----
in 4N ethanolic HCl	576mμ	log E 4.57
	416-25	c.3.83
	---	----

Guaiazulene-3-nitrile:- (fig.7)	λ max.	$Log_{10}E$ Molar
in hexane	580m μ	log E 2.70
	379	4.01
	361	4.88
	312	4.50
	298	4.64
	247	4.50
in ethanol	560m μ	log E 2.82
	378	4.08
	310	4.59
	298	4.67
	246	4.55
in 2N ethanolic HCl	556-64m μ	log E 2.80
	425	2.97
	379	4.02
	---	----

Guaiazulene-3-glyoxylic acid:- (fig.8)		
in benzene	445-6m μ	log E 4.10
(better solvent than hexane)	---	----
in ethanol	546m μ	log E 2.71
	404	4.07
	321	4.40
	317	4.40
	280	4.10
	235-36	4.44
in 2N ethanolic HCl	425m μ	log E 3.62
	---	----

Methyl ester of guaiazulene-3-glyoxylic acid:- (fig.9)

	λ max.	$Log_{10}E_{Molar}$
in benzene	536-50mμ	log E 2.85
	314-15	4.11
	---	----
in ethanol	416mμ	log E 4.13
	327	4.36
	245	4.34

α-Guaiazulene-aldoxime:- (fig.10)

in hexane(9)/ethanol(1)	625mμ	log E 2.64
	385	4.06
	307-9	4.53
	255-8	4.27
in ethanol	620mμ	log E 2.67
	385	4.08
	308-10	4.54
	254-6	4.27
β-Guaiazulene-aldoxime	610mμ	log E 2.75
	389	4.06
	307-10	4.55
	244-5	4.57

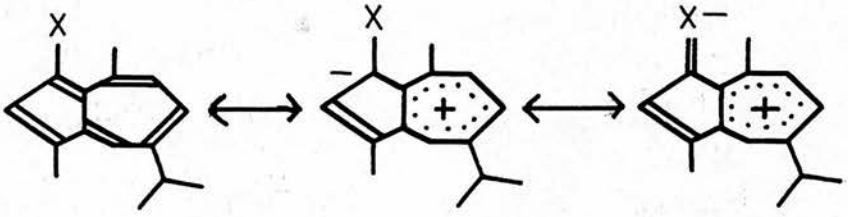
Nitro-guaiazulene:- (fig.11)

in hexane	564-70mμ	log E 2.73
	435-36	3.87
	417	3.95
	286	4.27
	238	4.41

Nitro-guaiazulene:- (fig.11) (Continued)

	λ max.	$Log_{10}E_{Molar}$
in ethanol	440-41mμ	log E 3.99
	322-24	3.98
	288-89	4.16
	236	4.28
in 2N ethanolic HCl	447mμ	log E 4.02
	324	3.99
	290	4.15
	238-39	4.39

With an electron attracting group, X, substituted in guaiazulene, the derivative may be written as:



The third form has no equivalent in the parent hydrocarbon. Such a contribution should result in a higher degree of polarisation of the molecule and can occur because of the presence of atoms more capable of accepting electrons than carbon.

	A	B	C	D	
X	λ max. mμ	λmax. mμ	λmax. mμ	λmax. mμ	Solvent
CHO	568	397	314,276	250	hexane
	538	401	318,279	251,238	ethanol
$CO.CH_3$	580	390	306	249	hexane
	560	397	311,277	240	ethanol
$CO.C_6H_5$	583	399	314,289	249	hexane
	566	413	325,289	240	ethanol
CO.Gu	582	407	316,298	242	hexane
	550	424	313,297	240	ethanol
CN	580	379,361	312,298	247	hexane
	560	378	310,298	246	ethanol
α-CH=NOH	625	385	308	257	hexane
	620	385	308	254	ethanol
H	605	367,350	285	246	hexane

[The bands in the spectra of guaiazulene-3-glyoxylic acid and its methyl ether cannot be tabulated in this way and are discussed separately]. From the table it is apparent that a hypsochromic shift is caused in the bands in column A, a bathochromic shift in

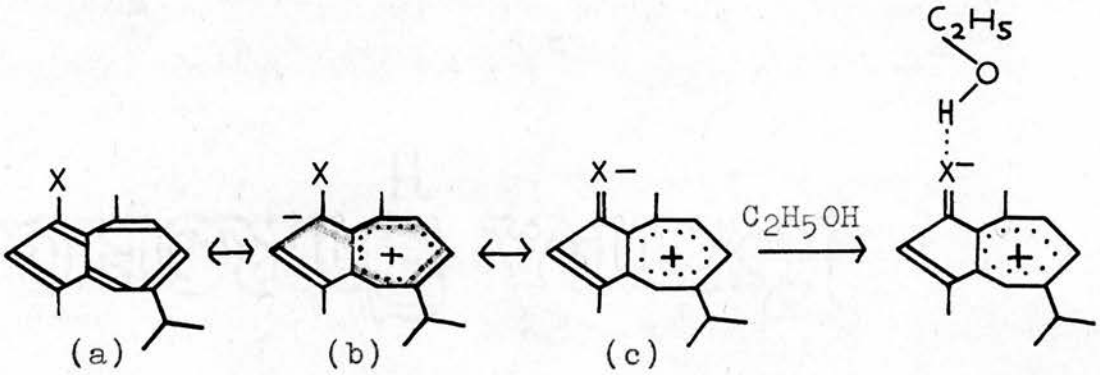
the bands in columns B and C, and very little change in those in column D; i.e. the excitation energy for the 'azulenic' band is increased and that for the 'ionic' band is decreased. This corresponds to the ability of the group, X, to attract electrons away from the azulene nucleus. The polarity of the molecules of these derivatives is also shown by the dependence of the spectra on the solvent employed. If the solvent is non-hydroxylic, an increase of solvent polarity causes a small hypsochromic shift in the A band. This is possibly due to alignment of the solvent molecules with the solute, so that polarisation of the latter by absorbed light requires more energy. The positions of the 'azulenic' maximum of guaiazulene-3-aldehyde and -3-nitrile in different solvents are:

Solvent	X=CHO	X=CN
hexane	568mμ	580mμ
benzene	560-66	570-72
ether	560	550

Although the actual change in the position of the maximum is small, the change in the absorption in the visible region is apparent to the eye, particularly in the above two compounds.

The polarisability of these guaiazulene derivatives containing electron attracting groups is shown by the comparison

of their absorption spectrum in a non-polar solvent with that in a hydroxylic solvent such as ethanol. Then hydrogen bonding with the solute can occur causing an increase in the importance of the form, LXXVIII(c)

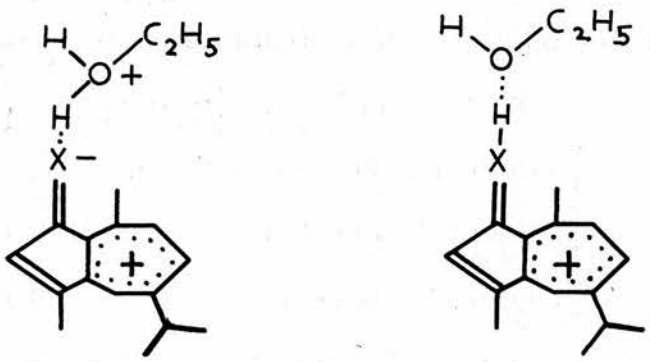


LXXVIII

The resulting change in the shape of the curve is particularly noticeable in nitro-guaiazulene (fig.11), where the 'azulenic' maximum becomes merely a point of inflexion. The possibility of intra- or inter-molecular hydrogen bonding in guaiazulene glyoxylic acid causes a difference in this compound which will be discussed later.

In ethanol containing hydrochloric acid two spectroscopically distinguishable processes may occur. (A) The protons may be in the form of oxonium ions involving water or ethanol and these hydrogen bond to the solute, LXXIX(a), or alternatively, (B), hydrochloride formation with the solute may take place whereupon the hydrogen atoms of the derived salt bond to the

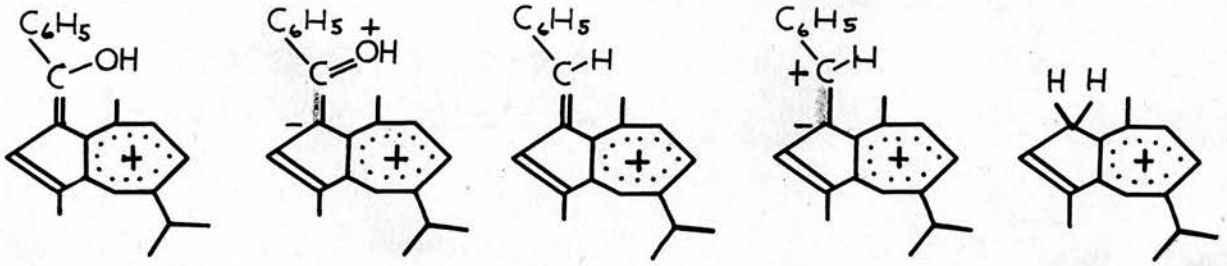
oxygen atoms of the solvent, as in LXXIX(b).



(a) LXXIX (b)

The former occurs with nitro-guaiazulene (fig.11) since the curve is not greatly changed from that obtained using pure ethanol as solvent. However with formyl, acetyl and benzoyl guaiazulene, (figs. 6, 3 and 4), the profound change requires the second interpretation. The A band falls and is replaced by an intense absorption which increases with acid concentration. Owing to the instability of the solutions at the low solute concentration required for measurement in the ultra violet region, the curves were not continued below 300mμ. In the case of guaiazulene nitrile (fig.7) the spectral change is not so pronounced. Since the imino state is probably less favoured than the enolic state this might be expected. It is not possible on the available evidence to make a decision as to the position of the protons since the spectrum is intermediate in character between that expected for either of the two extreme states.

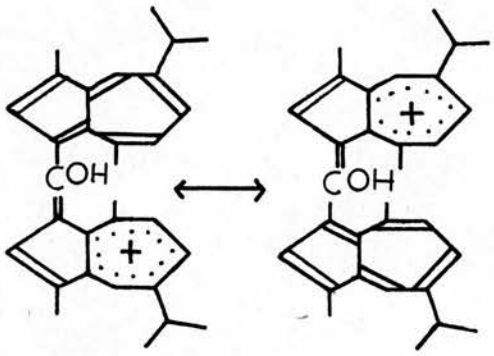
In the benzoyl compounds the new band of intense absorption must be due to the importance of the form LXXX(a). This is the hydroxy analogue of the benzylidene-guaiazulenium cation, LXXXI, discussed in Section B which has a band in the same region, (fig.4). The 'ionic' band of guaiazulene (the longest wavelength band to be found in guaiazulenium cation, LIV) is still present in the spectra of both these compounds. This is because there continue to be contributions from forms LXXX(b) and LXXXI(b).



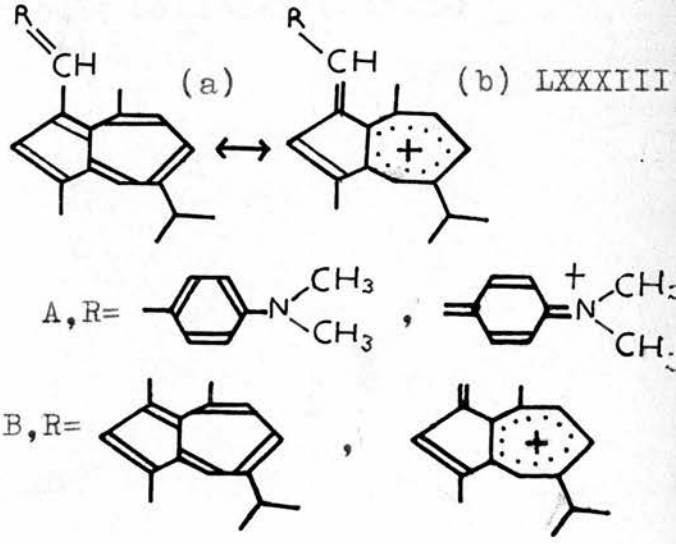
(a) LXXX (b) (a) LXXXI (b) LIV

Confirmation of this representation is provided by comparison of the spectrum of the isoelectronic substance benzylidene indene (Morton and de Gouveia. J.C.S., 1934, 911) with that of the benzylidene-guaiazulenium cation. The spectrum of the latter is obviously fulvenoid and the α-hydroxy-benzylidene-guaiazulenium cation must by analogy provide the best representation of the benzoyl guaiazulene hydrochloride. Similarly the acyl derivatives in general conform to this pattern.

Study of the effect of acid on diguaiazulyl ketone (fig.8) shows that band B is displaced to the same extent as in ethanol but that it decreases with rise in acidity. The new band which is introduced is at much longer wavelength than in the other carbonyl hydrochlorides and it lies over the original A band giving a purple colour. The height of this band increases with acid concentration and it may be concluded that the hydroxy-diguaiazulyl compound, LXXXII, formed by addition of a proton is responsible. Now this compound has a much more extended resonating system than that of LXXX (R=H, CHO,CH_3, or C_6H_5) and is comparable with the compounds LXXXIII (A and B) described in section B which have an intense blue colour.

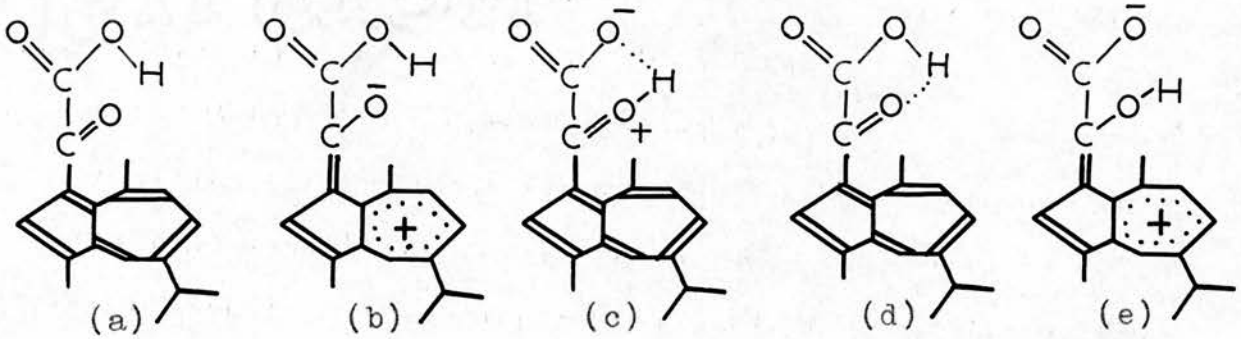


(a) LXXXII (b)



The interpretation of the spectra (figs.8 and 9) of guaiazulene glyoxylic acid and an ester (prepared by D.H. Reid) is rather difficult. The A bands in the spectra of both compounds in ethanol solution are hypsochromically shifted from

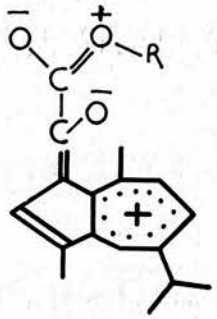
that of guaiazulene aldehyde in the same solvent but are of about the same intensity. Changing the solvent for the glyoxylic acid to benzene produces a considerable bathochromic shift in the B band which is the opposite of that expected from the compounds already discussed. With the ester the shift is in the normal direction but is very slight. From study of the aldehyde and acetyl and benzoyl guaiazulene it has been concluded that a bathochromic shift in the B band is due to hydrogen bonding of the carbonyl group with the solvent. Therefore it may be assumed that the large bathochromic shift with the glyoxylic acid in a non-hydroxylic solvent is caused by internal hydrogen bonding of the chelation type. The resulting molecule could be written with five major canonical forms, LXXI(a),(b),(c), (d) and (e).



LXXI

This should be a possible system because of the five-membered ring which would result, but dimer formation by means of hydrogen bonding is also possible.

The hypsochromic shift in the A band (compared with guaiazulene aldehyde) shown by both the ester and acid in a hydroxylic solvent must have a different cause. The necessary higher degree of polarisation that occurs in the aldehyde may be due to the contribution of a form, LXXI(f) produced by the electrostatic effect of the neighbouring methoxy or hydroxy group.



LXXI(f)

The fact that the hypsochromic shift on changing the ester from benzene to ethanol solution is small is probably also due to the proximity of the positively charged oxygen atom which is present in this form and to the steric masking of the carbonyl oxygen atom by the ester group. The spectrum of an ethanolic solution of the glyoxylic acid containing hydrochloric acid is unreliable because of instability.

Infra red spectra.

The values of the carbonyl vibrational frequencies of guaiazulene-3-aldehyde, acetyl and benzoyl guaiazulene and diguaiazulyl ketone are as follows:

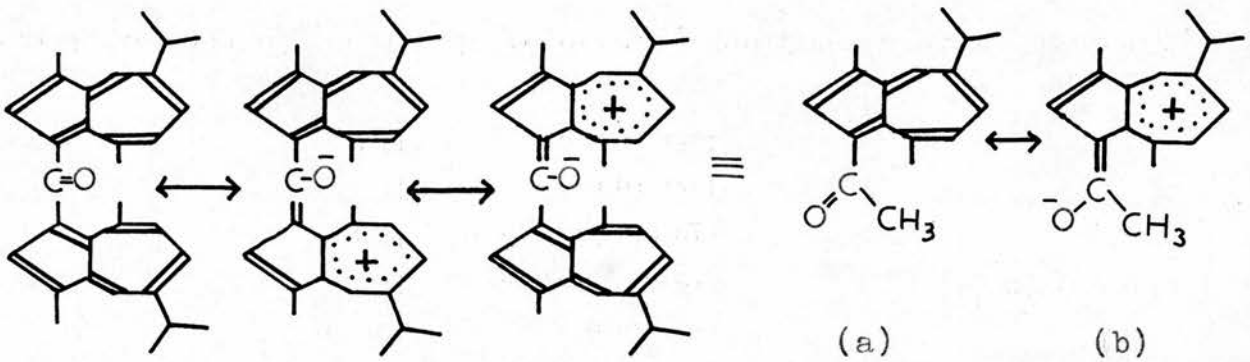
	CCl_4	EtOH	Nujol	KBr
acetyl guaiazulene	$1674cm^{-1}$	$1650cm^{-1}$		
	1658	1638		
benzoyl guaiazulene			1637	
guaiazulene aldehyde	1634	1614		1618
diguaiazulyl ketone	1616	1594		

These may be compared with the values:

acetone	$1723cm^{-1}$
acetophenone	1686
benzophenone	1655
tropone	1638
tropolone	1615

A reduction in vibrational frequency is found in each of these guaiazulene derivatives. This is due to an increase in the length of the C-O linkage through the partially polarised nature of the molecule. Diguaiazulyl ketone is in its place as the most polarised of the compounds, having three contributing forms, LXX (a), (b) and (c) whereas the others have only two. This is not obvious from the electronic absorption spectrum for the hypsochromic shift which the compound shows is the same as

that of the other two ketones. The probable reason is that in the forms with electron localisation on the oxygen atom, one of the guaiazulene nuclei remains in the 'azulenic' state.



(a) (b) (c) LXX

(a) (b) LXVIII

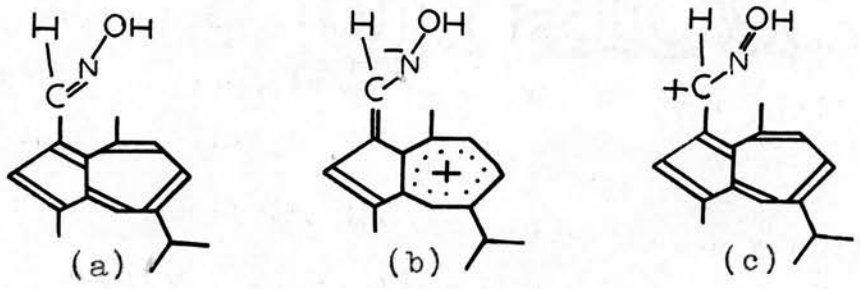
The fact that the values for the vibrational frequencies obtained in hydroxylic solvents are lower than those measured in carbon tetrachloride is another indication of the polarisability of these guaiazulene derivatives.

In guaiazulene-3-nitrile the C-N linkage is also shown to be polarised because of its low vibrational frequency (page 74).

guaiazulene nitrile	2183cm^{-1}
benzonitrile	2229

The list of characteristic frequencies, measured for guaiazulene nitrile is: 2183, 1550, 1534, 1520, 1412, 1328, 1299-90, 1209, 1157, 1122, 1099, 1055, 1019, 996, 959;
for nitro-guaiazulene (nujol): 1621, 1605, 1526, 1408, 1299, 1230, 1212, 1176, 1153, 1124, 1096, 1073, 1054, 1031, 1026, 1002, 955, 941, etc.

As already described, (p.70), the position of the values at 1650-1600cm^{-1} for the guaiazulene aldoximes led to assignment of configuration. The fact that they were lower than those of the benzaldoximes was used as evidence of the polarity of the C-N linkage, but this does not appear to be confirmed by the absorption spectra since the A band is bathochromically shifted in the α-guaiazulene aldoxime and is unchanged in the β-aldoxime. This anomaly may be explained by the fact that in these compounds two competing polarisations occur acting in opposite directions; cf. LVII(a), (b) and (c). Both (b) and (c) lengthen the C-N linkage and so lower the vibrational frequency. In the electronic spectrum forms (b) and (c) have an opposite effect and virtually cancel each other.



LVII

The overall effect of the α-aldoxime group, when the molecule is in hexane solution, is equivalent to the inductive influence of an alkyl group in the same position.

The list of the positions of the maxima in the infra red spectra are as follows:-

guaiazulene acetoxime: 3175, 1629, 1538, 1520, 1416, 1330, 1299, 1224, 1198, 1166, 1104, 1048, 1006, 984, 939, etc.

α-guaiazulene-aldoxime: 3195, 1605, 1543, 1520, 1408, 1333, 1290, 1217, 1205, 1176, 1166, 1121, 1103, 1087, 1056, 1027, 1016, 995, 944, etc.

β-guaiazulene-aldoxime: 3155, 1621, 1534, 1520, 1401, 1319, 1203, 1167, 1120, 1085, 1049, 1024, 994, 954, 934, etc.

α-guaiazulene-aldoxime hydrochloride: 2611, 2488, 1645, 1592, 1534, 1527, 1504, 1431, 1389, 1333, 1304, 1239, 1227, 1205, 1195, 1167, 1135, 1106, 1092, 1073, 1056, 1042, 1018, 998, 988, 968, 907, etc.

β-guaiazulene aldoxime hydrochloride: 2519, 1642, 1522, 1506, 1458, 1395, 1342, 1309, 1232, 1198, 1171, 1139, 1095, 1058, 1038, 1024, 999, 990, 968, 934, 911, etc.

The values underlined recur throughout the series and must be presumed to be due to the ring systems as a whole.

The reactivity of guaiazulene and the chemical properties and physical chemical measurements of derivatives containing electron attracting groups all show the polarity and polarisability of the molecules and lead to the conclusion that the view of the azulene nucleus as a fusion of a cycloheptatrienylium cation and a cyclopentadienylium anion is correct.

E X P E R I M E N T A L

E X P E R I M E N T A L

Melting points were determined on a Kofler block. The yields quoted in Part A are of material of analytical quality since they were required for spectrographic analysis. The chromatographic procedure was as follows: the ether extract containing the mixture to be separated was washed, with water unless otherwise stated, and dried over sodium sulphate. The solvent was removed by distillation and the residue, dissolved in petrol ether (b.p. 40-60°C.) or a mixture of petrol ether and a little benzene, was chromatographed on alumina. The solvents used for elution were petrol ether (b.p.40-60°C.), a mixture of petrol ether and benzene, benzene, a mixture of benzene and ether, ether, a mixture of ether and ethanol, and ethanol in that order. A mixture containing 7 volumes of benzene and 3 volumes of ether has been described by benzene(7)/ether(3). T.N.B. stands for 1:3:5-trinitrobenzene.

The Unicam S.P.500 was used to determine the absorption spectra and the S.P. 600 for qualitative measurements in the visible region. The infra red spectra were determined by Dr. Whitely and by Dr. Flett of I.C.I., Billingham, and Blackley respectively.

Dr. McLennan measured, by X-ray methods, the unit cells of certain of the compounds discussed. The densities of the appropriate crystals were determined by the flotation method using aqueous potassium mercuri-iodide to which it was found necessary in certain cases to add ethanol to "wet" the crystals.

Analyses were by Drs. Weiler and Strauss of Oxford.

Reaction of Guaiazulene with Mercuric Acetate.

In a preliminary experiment it was found that the addition of mercuric acetate in acetic acid to a solution of guaiazulene in the same solvent caused the colour to change to orange when reaction was complete. Removal of the solvent by distillation was attended with decomposition and although attempts were made to replace the mercuri-acetate group by iodine by warming no recognisable product could be isolated.

In later experiments a solution of guaiazulene in petrol-ether was shaken with an aqueous solution of mercuric acetate (saturated). Repeated extractions with fresh portions were made until the blue colour had completely gone from the organic layer. The bright orange/yellow aqueous phase was then filtered and added to an aqueous solution of an inorganic chloride. In initial work calcium chloride was used but it was found that the yellow precipitate first formed rapidly turned blue due to the reformation of guaiazulene. Finally barium chloride was used for the sample analysed. The precipitate was quickly filtered and washed with water and acetone. The latter removed mercuric chloride, adhering water and guaiazulene. A final washing with petrol-ether removed much of the blue colour remaining. Although the material should obviously be yellow a greenish yellow was normal for the product. The yield was

very dependent on the rate at which the solid was isolated but if the guaiazulene recovered was taken into account it was very high.

(Found: C, 31.2; H, 2.7; Cl, 12.0. $C_{15}H_{17}HgCl$ requires C, 41.5; H, 3.9; Cl, 8.2. $C_{15}H_{16}Hg_2Cl_2$ requires C, 27.0; H, 2.4; Cl, 10.6. $C_{15}H_{17}HgCl{\cdot}{\cdot}{\cdot}{\cdot}HgCl_2$ requires C, 25.5; H, 2.4; Cl, 15.1%).

Attempted benzoylation of guaiazulene mercuri-chloride.

In a preliminary experiment the mercuri-chloride was dissolved in AR pyridine giving a blue/green solution which changed to blue on addition of 2 moles of benzoyl chloride. After heating to boiling, the solution was poured into water with formation of a blue solid and a colourless solution. The solid was collected, washed with ethanol and then with ether which removed a green compound leaving a residue of pyridine mercuri-chloride. The ether solution was dried (Na_2SO_4) and taken to dryness. The residue was extracted with petrol ether in which part was soluble. Chromatography of the extract revealed the presence of guaiazulene and a green material (petrol ether(1)/ benzene(1)) which did not crystallise.

The ether soluble solid was extracted with chloroform leaving more pyridine mercurichloride, and the extract was taken to dryness and extracted with benzene. The residue was

crystallised from petrol ether/ethanol forming a finely divided red solid which did not melt below 310°C. Chromatography of the benzene solution separated a blue/green fraction (ether containing a trace of ethanol) which crystallised to a mixture of green and grey material and also a blue and a red band which could not be eluted by ethanol.

Preparation of 3-formyl-guaiazulene.

A suspension of zinc cyanide (5.9g.) in an ethereal solution (50 ml.) of guaiazulene (5.0g.) was saturated with dry hydrogen chloride. A red complex was deposited whose physical nature depended on minor details of procedure. After 15 hours this was decomposed in dilute hydrochloric acid in which it dissolved with considerable difficulty. When it was particularly insoluble successive and repeated warming with methylene dichloride and concentrated hydrochloric acid made it more tractable.

The red aqueous phase was separated from the blue ether phase, which was shown to contain a considerable quantity of guaiazulene, and after exhaustive extraction with ether, the red solution was made alkaline with sodium hydroxide. The resulting blue material was extracted into ether leaving a purple red aqueous phase from which the colour was removed by a second ether extraction. The two ethereal extracts were combined, and prepared for chromatography. It was necessary to add petrol

ether (b.p. 80-100°C.) before distilling off the ether, otherwise considerable decomposition occurred.

Elution (benzene containing a little ether) separated a brown band from a strongly adsorbed green band. The eluate which was purple yielded a dark red crystalline substance, (ethanol) m.p. 84-84.5 °C. Yield: 17.6% (Found: C, 84.7 and 84.6; H,7.7 and 7.9. $C_{16}H_{18}O$ requires C.84.9; H,8.0%). The aldehyde formed a 2:4-dinitrophenylhydrazone-red needles from acetic acid, m.p. 285°C.(dec.). (Found: C,66.0; H,5.54; N,13.3. $C_{22}H_{22}N_4O_4$ requires C,65.0; H,5.47; N,13.8%).

Formation of 3-hydroxymethylene-guaiazulenium chloride.

Dry hydrogen chloride was passed into a solution of 3-formyl-guaiazulene in ether. The hydrochloride was precipitated but could not be recrystallised and decomposed on heating. Analysis indicated that the 3-hydroxymethylene-guaiazulenium chloride had formed a hydrate. (Found: C,68.5; H,7.7; Cl,12.7. $C_{16}H_{18}O$, HCl, H_2O requires C,68.4; H.7.5; Cl,12.7%).

Formation of guaiazulene-3-aldoximes.

Guaiazulene-3-aldehyde (50mg.) was dissolved in ethanol (10ml.) containing 4 drops of 10% sodium hydroxide solution. Hydroxylamine hydrochloride (250mg.) was added and after boiling

under reflux for 5 minutes, the solution became blue. The boiling was continued for a further 25 minutes and the solution was diluted with water and then extracted with ether. The extract was prepared for chromatography in the normal manner. A trace of yellow material was first eluted (ether) and then a mixture of the two oximes as a green solution (ether(7)/ethanol(1)). This was rechromatographed and separation into two fractions occurred. Form I crystallised as green plates (petrol ether/ethanol) m.p. 128-130°C. (Found: C,79.4; H,8.0; N,6.0. $C_{16}H_{19}NO$ requires C,79.6; H,7.9; N,5.9%). Form II crystallised as green needles from ether/petrol ether (b.p.60-80°C.), m.p.162°C. (Found: C,79.2; H,7.9; N,5.8%). Total yield of oximes: 40 mg.; 80%. Less than 5% of the aldoxime mixture was in form II.

Using an ethanolic solution of the aldehyde made definitely alkaline, small quantities of unchanged aldehyde and of guaiazulene-3-nitrile were present. It was necessary to boil the mixture for 3 hours instead of 30 minutes.

An alternative preparation used the crude extract from the aldehyde preparation before chromatography. An ethanolic solution of hydroxylamine hydrochloride and sufficient 10% sodium hydroxide was added to make it alkaline and the ether was removed by distillation. The procedure used for oxime formation from the aldehyde was then followed. The products were a smaller proportion of the nitrile and the two oximes, but no aldehyde.

Total yield of oximes: 37% with respect to initial guaiazulene.

Formation of guaiazulene-3-aldoxime I hydrochloride.

Dry hydrogen chloride was passed into a solution of guaiazulene aldoxime I in ether. The red solid which was immediately precipitated changed in part to purple on the filter. The mixed solid, m.p.135-145°C.(dec.) was analysed in the crude state. (Found: C,68.6; H,6.2; N,4.7; Cl,11.6. $C_{16}H_{20}NOCl$ requires C,69.1; H,7.3; N,5.0; Cl,12.8%).

Freshly prepared aldoxime I hydrochloride was decomposed with 5% aqueous sodium hydroxide, and the blue oxime was extracted into ether. After the usual preparation, chromatography of the residue separated a small quantity of aldoxime I, m.p.125°C., from a large proportion of aldoxime II which crystallised as green needles (ether/petrol ether), m.p.162°C. (Found: C,79.2; H,7.9; N,5.4. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N,5.8%).

Formation of guaiazulene-3-aldoxime II hydrochloride.

The hydrochloride was prepared in the same way as aldoxime I hydrochloride. It was a purple crystalline solid, m.p. 138-140°C.(dec.). (Found: C, 69.4; H, 7.3; N,5.0; Cl,12.4. $C_{16}H_{20}NOCl$ requires C, 69.1; H,7.3; N,5.0; Cl,12.8%).

X-ray powder photographs of the two hydrochlorides showed

them to have different crystal structures.

Decomposition of guaiazulene-3-aldoxime II hydrochloride with alkali as above gave only aldoxime II.

Action of dilute hydrochloric acid on guaiazulene aldoxime I.

Guaiazulene aldoxime I (50mg.) was dissolved in ethanol (10ml.); dilute hydrochloric acid (10ml.) was added and the solution was boiled under reflux for 40 minutes at the end of which its colour was green. It was poured into water and the solution was extracted with ether. The blue extract, washed with dilute sodium carbonate solution and with water, was dried and taken to dryness. Chromatography of the residue yielded a large quantity of a blue compound which was eluted by petrol ether. A T.N.B. complex was formed, purple needles, m.p.147-149.5°C. (Authentic guaiazulene T.N.B. 149°C.). The chromatogram also gave small quantities of orange and red material and a green fraction (ethanol) which turned red on dilution with water.

Action of methyl iodide on guaiazulene aldoximes.

A solution of guaiazulene-3-aldoxime I (586mg.) in methyl iodide (25 ml.) was boiled under reflux for 30 minutes. The methyl iodide was distilled off and the residue chromatographed on alumina. A little guaiazulene was first eluted and then a

purple solution (benzene(7)/ether(3)). The solvent was evaporated under reduced pressure and the residue crystallised from ethanol as green needles melting to a purple liquid, m.p.64.5-68°C. Yield: 75mg., 13.8%. The material, purified by sublimation under reduced pressure in a boiling water bath, had m.p.64-65.5°C. (Found: C,85.7; H,7.8; N,7.0. Guaiazulene-3-nitrile, $C_{16}H_{17}N$, requires C,86.1; H,7.7; N,6.3%). Guaiazulene nitrile is very soluble in all the common organic solvents. An orange band was eluted as a purple solution (ether) from which a red brown solid was obtained (ethanol), m.p.84-85°C. Yield: 10mg.,1.8%. (Found: C,83.6; H,7.9; N,0.8. Guaiazulene-3-aldehyde, $C_{16}H_{18}O$, requires C,84.8; H,8.0%). 40% of the aldoxime I was recovered.

The same products, guaiazulene nitrile and aldehyde and the corresponding aldoxime II, were obtained when the latter was boiled under reflux with methyl iodide under the same conditions.

Action of methyl magnesium iodide on guaiazulene-3-nitrile.

Guaiazulene nitrile dissolved in dry ether was added to an equivalent quantity of methyl magnesium iodide in the same solvent at room temperature. After 20 minutes the mixture was poured into a saturated solution of ammonium chloride, and the products ether extracted. After the usual preparation chromatography yielded guaiazulene and the nitrile. In a second

experiment a similar mixture was boiled for 1 hour, but the products were the same. Finally, one hundred times the required quantity of methyl magnesium iodide was used. The mixture was boiled for 5 hours and the following day it was hydrolysed by pouring into saturated ammonium chloride solution. There was no evidence of attack by the reagent other than the presence of a trace of guaiazulene.

Action of acetic anhydride on guaiazulene-3-aldoxime.

Guaiazulene aldoxime I (50 mg.) was mixed with acetic anhydride (5ml.) containing a drop of concentrated sulphuric acid. After 3 hours the solution, which had changed from orange to olive yellow, was poured into water. The products were extracted into ether which was washed with 5% aqueous sodium carbonate and treated normally. The residue was chromatographed on alumina. The products were the same as those formed by the action of methyl iodide.

Action of acetonitrile on guaiazulene.

In a preliminary experiment acetonitrile (1.2 moles) was added to a solution of guaiazulene (1 mole) in dry ether saturated with hydrogen chloride. When zinc chloride (2 moles) was added, the colour changed to green and a yellow solid

separated. The solution was poured next day into dilute sulphuric acid and the blue ether phase was separated. The aqueous solution was heated to decompose any complex and was re-extracted with ether. Finally it was made alkaline and again ether extracted. The combined extracts contained only guaiazulene. In a second experiment methylene dichloride was used as solvent and aluminium chloride in place of zinc chloride. The complex was decomposed with water, but again there was no azulenic material present other than guaiazulene.

Acetylation of guaiazulene using no catalyst.

Excess acetyl bromide (0.7ml.) was mixed with a solution of guaiazulene (777mg.) in petrol ether (b.p.60-80°C.) (0.8ml.) and the solution was kept for 24 hours at room temperature. The resulting brown complex was decomposed with 50% aqueous ethanol, and the solution exhaustively extracted with ether. The ethereal extract was prepared for chromatography.

The first eluate was a green solution (petrol ether) from which no crystalline material could be obtained. On rechromatography it decomposed to a mixture of yellow green compounds. The residue, on removal of the solvent from the original green eluate, was boiled in ethanol with T.N.B., giving purple needles in yellow mother liquors. The complex was recrystallised from ethanol, m.p.144-146.5°C. (Found: C, 61.4; H,5.28; N,10.1. The

T.N.B. complex of an isomer of guaiazulene, $C_{21}H_{21}N_3O_6$, requires C,61.3; H,5.16; N,10.2%). Addition of acetone to the purple complex regenerated a blue/green hydrocarbon. The T.N.B. complex (1.2g.) was dissolved in glacial acetic acid (50ml.) and stannous chloride (2.75g.) and concentrated hydrochloric acid (3ml.) added. The solution was kept at 80°C. It turned brown in a few minutes, and after 2 hours was poured into water and the azulenic material was extracted into ether. The extract was washed with water and dried, and the solvent removed by distillation leaving blue oily drops which were distilled at 0.8mm. pressure in a boiling water bath. The blue distillate contained some T.N.B. complex and did not crystallise. It was resublimed with the water bath at 60°C. The spectrum of the resulting blue liquid was determined and X-ray powder photographs of the T.N.B. complex and that of guaiazulene were compared.

A second product was eluted (benzene) and rechromatographed. It crystallised from petrol ether/ethanol as purple plates, m.p. 85.5-86°C. Yield: 349mg.,37%. (Found: C,84.6; H,8.2; $C_{17}H_{20}O$ requires C,85.0; H.8.5%). A T.N.B. complex was obtained as red needles, m.p. 124°C., and the 2:4-dinitrophenylhydrazone as red needles, m.p.109-110.5°C. (Found: C, 65.7; H, 5.70; N, 10.9. $C_{23}H_{24}N_4O_4$ requires C,65.7; H,5.72; N.13.3; O,15.2%).

An experiment using a guaiazulene solution in petrol ether at higher dilution produced a much lower yield of acetyl guaiazulene, but using guaiazulene (800mg.) dissolved in methylene

dichloride (6ml.) and acetyl bromide (750 mg.), a yield of 42.5% was obtained, along with a blue/green hydrocarbon which formed a purple T.N.B. complex.

Acetylation of guaiazulene using acetic anhydride and a catalyst.

Guaiazulene (3.2g.) was dissolved in carbon disulphide (36ml.) and acetic anhydride (3.6g.) and stannic chloride (3.0g.) added. The mixture was boiled under reflux for 7 hours and then the complex was decomposed with dilute hydrochloric acid. The products were ether extracted and prepared for chromatography. The same green hydrocarbon fraction and acetyl guaiazulene were separated. Yield: 42%.

Action of trichoracetic acid on acetyl guaiazulene.

Acetyl guaiazulene was mixed with ten times its weight of trichloracetic acid and the mixture was heated until molten in a water bath at 60°C. The red mixture was made alkaline with dilute ammonia and the solution was extracted with ether. The resulting blue ethereal solution was washed with water sodium carbonate and then treated normally. A large quantity of guaiazulene was eluted (petrol ether). Brown decomposition products were also present.

Condensation of acetyl guaiazulene with phenylhydrazine.

In a preliminary experiment excess phenylhydrazine was added to a solution of acetyl guaiazulene in 10% ethanolic acetic acid. The solution was warmed for a few minutes and then it was filtered to remove crystals of phenylhydrazine acetate. It was poured into water and ether extracted. The extract was then prepared for chromatography. The largest fraction, blue/green in colour (petrol ether) was rechromatographed but did not crystallise. The liquid was analysed, (Found: C,83.7; H,4.1; N,8.5. $C_{23}H_{26}N$ requires C,83.7; H,7.8; N,8.5%), and then boiled under reflux in an excess of methyl iodide for 2 hours. The solution was taken to dryness and the residue extracted with petrol ether leaving a red methiodide adhering to the walls of the flask.

Formation of oxime from acetyl guaiazulene.

In a preliminary experiment molar quantities of acetyl guaiazulene and hydroxylamine hydrochloride were dissolved in ethanol and the solution was made alkaline with 10% aqueous sodium hydroxide. After boiling under reflux for 1.5 hours the solution was poured into water and ether extracted and the extract treated normally. Chromatography showed the presence of a trace of blue material (ether (9) / ethanol (1)) as the

only product besides acetyl guaiazulene. In a second experiment pyridine was used as solvent for acetyl guaiazulene and excess hydroxylamine hydrochloride. The mixture was heated in a boiling water bath for 3 hours and the products were the same.

Using a superior method, acetyl guaiazulene (550mg.) was dissolved in AR pyridine (80ml.) and hydroxylamine hydrochloride (240mg.) was added. The solution was boiled under reflux for 1.25 hours and a further 330mg. of hydroxylamine hydrochloride was then added; the heating was continued for a further 30 minutes. The solution was poured into water and the mixture ether extracted. The extract was washed with dilute hydrochloric acid until the washings were colourless and were prepared for chromatography in the normal way. Acetyl guaiazulene (benzene) was separated from a blue compound (ether). This crystallised as blue plates (petrol ether/ethanol) m.p. 140-141.5°C. Yield: 245mg., 42%. (Found: C,79.7; H,8.3; N,5.5. $C_{17}H_{21}NO$ requires C.80.0; H,8.3; N,5.5%). A lower yield (15.1%) was obtained when a similar reaction mixture was kept at 100°C. for 2 hours, more hydroxylamine hydrochloride added and the solution boiled under reflux for 30 minutes.

Formation of guaiazulene-3-acetoxime hydrochloride.

Dry hydrogen chloride was passed into a solution of the

acetoxime in ether. Red needles were immediately dsposited, m.p. 110-120°C. (dec.), and analysed in the crude state. (Found: C,69.7; H,8.8; N,4.2; Cl.11.7. $C_{17}H_{22}NOCl$ requires C,69.9; H,7.6; N,4.8; Cl.12.2%).

Action of methyl iodide on guaiazulene acetoxime.

The acetoxime (720mg.) was dissolved in methyl iodide (15ml.) and the solution was boiled under reflux for 3 hours. The following day the methyl iodide was removed by distillation and the residue was chromatographed, giving three unstable blue fractions (benzene(1)/ether(1)), (ether(9)/ethanol(1)), (ether(1)/ethanol(1)). The first solution decomposed on distillation at reduced pressure and formed a yellow very unstable compound, λmax.328-332mμ on addition of dilute hydrochloric acid. It was not present in a second experiment. The second lost its characteristic colour (λmax.c.598mμ) becoming brown within a few minutes. On addition of dry ether, saturated with hydrogen chloride it turned orange, λmax.401mμ, with very high absorption. The third fraction was red in transmitted light, λ max.c.600mμ. It was very unstable with a strong smell of methylamine, and decolourised completely overnight. It could not be extracted into alkali, but changed to orange λmax.394mμ with very high absorption on addition of

hydrogen chloride. The reaction appeared to be reversible.

Action of phenyl magnesium bromide on acetyl guaiazulene.

A red complex was formed immediately when a solution of acetyl guaiazulene in dry ether was added to a solution containing an excess of phenyl magnesium bromide. The mixture was boiled under reflux for 40 minutes during which the colour changed to yellow brown. The complex was decomposed by addition of 0.05N hydrochloric acid giving a yellow/green aqueous solution which extracted brown into ether. Chromatography showed this to contain guaiazulene, unchanged acetyl guaiazulene and two yellow/brown components.

Action of benzyl magnesium bromide on acetyl guaiazulene.

Zimmermann's method (Thesis, Eidg.Techn.Hochschule, Zurich, 1953) was applied to react benzyl magnesium bromide with acetyl guaiazulene. The products were all non-azulenic, orange or yellow in colour.

Condensation of acetyl guaiazulene with aromatic aldehydes under alkaline conditions.

Acetyl guaiazulene (220mg.) and benzaldehyde (150mg.) were added to ethanol (12ml.) containing sodium ethoxide, and the

solution was boiled under reflux for 2 minutes. The red brown solution (brighter red in concentrated hydrochloric acid) was poured into water, ether extracted, and the extract prepared for chromatography. A brown band was eluted (benzene(1)/ether(1)) as a green solution which was orange red in transmitted light. A red 2:4-dinitrophenylhydrazone, m.p.243°C., was prepared. Unchanged acetyl guaiazulene, yellow and brown fractions and a green solution, red in transmitted light, (ether(9)/ethanol(1)) were also present.

Similar reactions were carried out using o-hydroxy and o-amino -benzaldehydes, but although they formed red solutions the results were inconclusive.

A larger proportion of the green fraction, red in transmitted light was obtained when ethanol containing 0.75% sodium hydroxide was used and the mixture was allowed to stand at room temperature for 3 days. The compound did not crystallise. Addition of picric acid gave a greenish brown suspension.

Using o-amino-benzaldehyde and the same conditions, a green fraction, red in transmitted light, was obtained along with unchanged acetyl guaiazulene, a trace of guaiazulene and a number of other fractions. It was distilled at 0.6mm. and 200°C. giving a blue solid, m.p.180-181°C., insoluble in benzene, and a yellow green benzene soluble compound. There was insufficient

of the blue compound for analysis (from 600mg. acetyl guaiazulene). It had absorption maxima at 610 and 368 mμ. In dilute hydrochloric acid it became colourless, λ max. 365mμ and turned green, λ max. 705 and 315mμ after standing for three days.

Condensation of acetyl guaiazulene with aromatic aldehydes under acid conditions.

Acetyl guaiazulene (400mg.) was dissolved in a mixture of ethanol (19ml.) and bench dilute hydrochloric acid (1ml.), and benzaldehyde (400mg.) was added. The solution was warmed to 40°C. and allowed to stand at room temperature overnight. On pouring into water, a blue solution was formed which extracted into ether giving a purple solution leaving an orange aqueous phase. No red colour was formed by addition of concentrated hydrochloric acid to the extract. A small amount of the green material, red in transmitted light, was shown to be present with unreacted acetyl guaiazulene. The aqueous phase was extracted with chloroform and the extract dried. To it was added a saturated solution of hydrogen chloride in ether which precipitated a red solid, m.p. c.115°C. It was dissolved in alkali and reprecipitated, after which the m.p. was above 320°C. From the crude hydrochloride a picrate was formed - a dark red solid, m.p.111-112°C.(dec.).

Salicylaldehyde (0.36ml.) was added to a solution of acetyl guaiazulene (730mg.) in ethanol containing 5% of hydrochloric acid and the solution was boiled under reflux for 2 hours. It was poured into water and the red solution was extracted with chloroform. The extract was washed with water, dried and taken to dryness. The residue was dissolved in ethanol and less than the equivalent quantity of picric acid added. The concentration of the solution by distillation under reduced pressure yielded a dark red solid, m.p.108-118°C. Yield: 570mg. It decomposed during recrystallisation.

Condensation of guaiazulene with cinnamoyl bromide.

When cinnamoyl bromide (1g.) was added to a solution of guaiazulene (1g.) in methylene dichloride (30ml.) a violet colour was formed within a few minutes. After 2 days at room temperature the solution, which had become red, was poured into water. The aqueous phase was green. The mixture was extracted with chloroform and the extract was washed, dried, and distilled to dryness under reduced pressure. Part of the residue was soluble in petrol ether and was chromatographed on alumina. Guaiazulene and a green hydrocarbon fraction (purple T.N.B. complex) were eluted by petrol ether. The major components were a green compound which formed a blue band, and a yellow/green

compound which formed a band whose colour changed from brown through red to orange with increased polarity of the solvent. Both were eluted by a mixture of equal parts of benzene and ether. Rechromatography separated the two components completely. Neither crystallised. The latter formed a red water soluble compound in concentrated hydrochloric acid, and a yellow solid m.p.100-120°C. with 2:4-dinitrophenylhydrazine.

Preparation of benzoyl guaiazulene using a catalyst.

In preliminary attempts to react guaiazulene with benzoyl chloride using aluminium chloride as catalyst and petrol ether (b.p.60-80°C.) as solvent it was found necessary to heat the mixture, but even so, low yields were obtained. The best method was as follows: Guaiazulene (9.78g.) was dissolved in petrol ether (b.p.60-80°C.)(60ml.) and benzoyl chloride (10.4g.) and aluminium chloride (13.5g.) were added. Heat was evolved and a red complex was formed when the components were mixed. The mixture was boiled under reflux for 15 minutes. The complex, which was completely soluble, was decomposed by pouring the solution into 0.5% hydrochloric acid. The mixture was extracted with petrol ether until the aqueous layer was colourless, and the extract was washed with water and dried, concentrated by distillation and chromatographed on alumina.

A brown band was eluted (petrol ether) as a blue/green solution. When it was concentrated benzoyl guaiazulene separated out and was collected. The mother liquors were chromatographed giving a blue green oily solid (λ max.620mμ) which decomposed on rechromatography to six fractions, among them guaiazulene. The second component (benzene(1)/ether(1)) was green in reflected light and red in transmitted light and proved to be benzoyl guaiazulene. It yielded violet crystals, m.p.120-121°C. (petrol ether/ethanol) (Found: C,87.0; H,7.03. $C_{22}H_{22}O$ requires C,87.5, H,7.28%). The mother liquors which formed a tar when concentrated and a third green fraction (ethanol) were combined and rechromatographed giving a small quantity of benzoyl guaiazulene along with guaiazulene and a brown decomposition product. The total yield of benzoyl guaiazulene was 1.5g.,10%.

No dinitrophenyl hydrazone or T.N.B. complex could be prepared.

Preparation of benzoyl guaiazulene using no catalyst.

Guaiazulene (571mg.) was dissolved in petrol ether (b.p. 80-100°C.)(8ml.), benzoyl bromide (0.82ml.) was added and the solution boiled under reflux for 4.5 hours. The complex was decomposed with 50% aqueous ethanol and the solution was ether extracted. The extract was treated in the normal manner.

A green eluate, blue in transmitted light (benzene(1)/ether(1)) yielded purple plates m.p.120-121°C.(ethanol). Yield: 68.5mg.,8%. The mixed m.p. with the product from the reaction using benzoyl chloride and aluminium chloride as catalyst was 119.5-121°C.

Action of methyl magnesium iodide on benzoyl guaiazulene.

In preliminary experiments benzoyl guaiazulene was added to a solution of excess methyl magnesium iodide in dry ether. In one, the mixture was boiled under reflux for 2 hours, and in another it was kept at room temperature for 6 hours before the complex was decomposed by addition of 0.5% hydrochloric acid. In neither case was unchanged benzoyl guaiazulene or other azulenic material present.

Action of lithium aluminium hydride on benzoyl guaiazulene.

In a series of preliminary experiments benzoyl guaiazulene was dissolved in dry ether and 2 moles of lithium aluminium hydride added. In the first, the solution which had changed to brown was boiled under reflux for 1 hour before dilution with water and extraction with ether. The extract contained unchanged benzoyl guaiazulene and a very small quantity of a blue/green compound (λ max.605-610mμ) eluted by ether containing a trace of ethanol. Addition of dilute hydrochloric acid converted it to a yellow solution (λ max.371-373mμ) which could

not be extracted with chloroform. In a second experiment, 4 moles of lithium aluminium hydride were used and the mixture boiled under reflux for 2 hours before addition of water. No benzoyl guaiazulene remained, but a larger quantity of the blue/green compound whose purple T.N.B. complex was unstable, and a yellow decomposition product were present. During an experiment when 2 moles of lithium aluminium hydride was used, the ether boiled away during heating for 1 hour on a boiling water bath, consequently the reactants were heated dry at 100°C. for part of the time. One product was a blue/green compound (λmax.625mμ) (petrol ether(9)/benzene(1)). In ethanol it formed a green solution which was converted to a dull pink when boiled with T.N.B. The other product was yellow (ethanol).

Condensation of guaiazulene with benzyl chloride.

A series of experiments was carried out using the reactants in the proportions 1 mole of guaiazulene to 1.5 moles of benzyl chloride but in different solvents. Since boiling them alone under reflux for 5.5hours in benzene produced no reaction, aluminium chloride (0.2 moles) was used as catalyst in the following experiments. An insoluble tar was formed when the mixture was boiled for 2 hours in nitrobenzene or tetralin. As a milder condition, petrol ether (b.p.60-80°C.) was employed, and the solution boiled under reflux for 15 minutes after standing

at room temperature for 30 minutes. The ether soluble portion of the material after addition of 0.5% dilute hydrochloric acid consisted of guaiazulene and orange decomposition products. The insoluble portion was dissolved in ethanol, taken to dryness and was distilled at 0.6mm. and 50-60°C. Chromatography showed the distillate to contain a small quantity of a blue/green oil (petrol ether(1)/benzene(1)).

Solvents were then used in which the complex was more soluble. With methylene dichloride, the solution was kept at room temperature for 45 minutes and then boiled under reflux for 30 minutes. No blue material other than guaiazulene was present. However, boiling the mixture under reflux in ethylene dichloride for 2.25 hours and then pouring the solution into 0.5% hydrochloric acid produced a green organic phase which on chromatography was shown to contain a blue component (petrol ether) (λmax.630-635mμ) which was mixed with guaiazulene, and also some decomposition products. The aqueous phase was purple, blue when diluted with water. It became colourless on addition of alkali and reverted to blue on adding acid. The blue colour was extracted into chloroform giving a blue/green solution (λmax.562-564mμ).

In a final experiment, a trace of stannic chloride was used as catalyst, and methylene dichloride as solvent. The mixture was boiled under reflux for 3 hours and poured into

0.5% hydrochloric acid. Extraction with ether left a blue aqueous phase. The green organic phase was prepared for chromatography. It was possible to separate by rechromatography some of the second blue hydrocarbon from the guaiazulene which was the first to be eluted by petrol ether. Blue/green crystals were obtained, m.p.56-57.5°C. (Found: C,90.4; H,8.2. Benzyl guaiazulene, $C_{22}H_{24}$, requires C,91.5; H,8.4%; diguaiazulyl ethane, $C_{32}H_{38}$, requires C,91.0; H,9.1%).

Action of oxalyl chloride on guaiazulene.

(a) using methylene dichloride as solvent.

Oxalyl chloride (290mg.) was run slowly into a solution of guaiazulene (460mg.) in methylene dichloride (5ml.) and the solution was kept at 25°C. for 2 hours. The homogenous mixture became deep reddish purple, and vigorous evolution of a gas, acid to litmus, occurred. The mixture was hydrolysed by pouring into water, and allowed to stand overnight. The solution was extracted with ether and the extract washed free of acid. Exhaustive washing revealed the presence of no azulenic acid. The ether extract was treated normally and chromatographed. Guaiazulene (130mg.28%) was eluted (petrol ether) then a brown band (benzene) from which the ketone was obtained as dark green needles, m.p. 189-191°C. (ethanol). Yield: 70mg.,14.3%. (Found: C,87.5; H,8.1. $C_{31}H_{34}O$ requires C,88.1; H,8.1%).

A second experiment was carried out using guaiazulene (540mg.) dissolved in methylene dichloride (5ml.) and oxalyl chloride (340mg.) but the mixture was allowed to stand for 12 hours before being hydrolysed. The yields were: 57.4% guaiazulene; 13.0% diguaiazulyl ketone. There was no trace of an azulenic acid.

(b) using petrol ether as solvent.

Oxalyl chloride (305mg.) was run into a solution of guaiazulene (480mg.) in petrol ether (b.p.60-80°C.)(5ml.) and the mixture was kept for 2.25 hours at 25°C. The solvent became red while a slow evolution of gas, acid to litmus, was observed. A brown complex gradually settled out at the bottom of the flask, and the mixture was treated as in the previous experiment. On complete removal of hydrochloric acid by washing with water, the washes became orange red in colour. The ether extract was therefore washed till the washes were no longer orange coloured and prepared for chromatography.

The first compound to be eluted was guaiazulene (190mg.). This was followed by a narrow, light helio band (petrol ether(10)/benzene(1)). It yielded 20mg. of a blue liquid which was further purified by formation of a T.N.B. complex. This was decomposed on an alumina column, the blue compound being eluted by petrol ether, and then rechromatographed giving a deep blue solution. Yield: 4.2%. The T.N.B. complex was a chocolate

brown microcrystalline solid, which decomposed before the m.p. 125-129°C.(not sharp). Diguaiazulyl ketone was eluted from the column by benzene. Yield: 75mg.,14.7%.

On addition of hydrochloric acid to the aqueous orange red solution and extraction with ether, a red ethereal extract was obtained. This was re-extracted into 2N sodium hydroxide and the alkaline solution washed once with ether and reacidified with acetic acid. Enough concentrated hydrochloric acid was added to cause complete precipitation of the glyoxylic acid. After allowing the acid solution to stand for 2 hours at 0°C., complete precipitation of the guaiazulene glyoxylic acid had occurred as fine reddish brown needles, m.p.115-116°C. Yield: 150mg.,22.9%. (Found: C,75.5; H,6.7%. $C_{17}H_{18}O_3$ requires C,75.5; H,6.7%).

Preparation of nitroguaiazulene.

Guaiazulene (200mg.) was dissolved in carbon tetrachloride (20ml.) in an ice bath and tetranitromethane (200mg.) dissolved in 20ml. of the same solvent was slowly added. Immediate colour change to brown occurred. After 30 minutes the temperature was allowed to rise, the solution was taken to dryness, and the residue chromatographed. The product was a red brown compound (benzene(9)/ether(1)) which crystallised in brown plates from petrol ether, m.p. 72°C. Yield: 61mg.25%. (Found: C,74.2; H,7.3; N,5.6. $C_{15}H_{17}NO_2$ requires C,74.1; H,7.0; N,5.8%). It is very

soluble in the common organic solvents tested. The same yield was obtained using 120mg. tetranitromethane (0.6 mole) in place of 200mg., the molar quantity.

In a third experiment, 60mg. tetranitromethane (0.3 moles) was used. The colour changed rapidly to green on mixing but did not go through to brown. The chromatogram separated guaiazulene (37mg.), nitroguaiazulene (52mg.) and a purple band (ether) from which green needles were obtained (petrol ether), m.p.82-85°C. (Found: C,84.5; H,8.0; N,0. Guaiazulene-3-aldehyde, $C_{16}H_{18}O$ requires C,84.8; H,7.6%). The mixed m.p. with a sample of guaiazulene aldehyde was 82-83°C. The aldehyde was present in very small quantity, but a 2:4-dinitrophenylhydrazone was prepared and the positions of the first absorption maxima in hexane and ethanol determined.

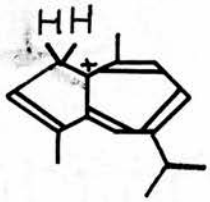
Reduction of nitroguaiazulene with lithium aluminium hydride.

Nitroguaiazulene (60mg.) was dissolved in dry ether (6ml.) in an ice and salt bath at -10°C. and lithium aluminium hydride (10mg.) was added. The solution was kept in the bath for 10 minutes and then the temperature allowed to rise. While gaining room temperature, effervescence occurred and an insoluble complex was formed. Saturated ammonium chloride solution was added to decompose the complex, and a red material was extracted from the resulting solution by ether. The extract was prepared for chromatography. A trace of nitroguaiazulene was eluted first

(benzene), then a pale yellow fraction, and a large orange fraction (ether(1)/ethanol(1)). A brown band was present which was not eluted by ethanol.

S E C T I O N B

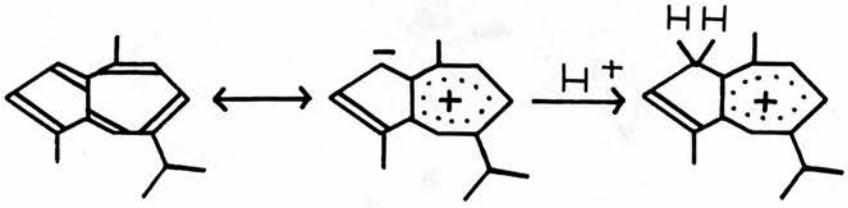
During preliminary studies towards a Gattermann reaction with guaiazulene (section A), it was observed that the hydrocarbon became colourless in presence of hydrogen chloride when dissolved in the non-hydroxylic solvent, methylene dichloride, (fig.1). It was considered by Plattner, Heilbronner and Weber (Helv.Chim.Acta,1952,35, 1036) and Heilbronner and Simonetta (Helv.Chim.Acta,1952, 35,1049) that in acid medium the azulenes form hydrochlorides with a methylene group on position-1,-(3), which they wrote as, e.g., LIV(b).



8 mesomeric forms

LIV(b)

Reid and Stafford (Chem. and Ind.,1954,277) describe this as occurring through the localisation of an electron pair on this carbon atom, and regard the change in colour as a reflection of the resulting loss of 'azulenic' resonance possibilities.



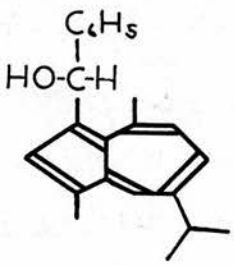
LIV(a)

Comparison of the guaiazulenium cation with N-alkyl picolinium salts and with indene suggested that the methylene group formed by addition of a proton to guaiazulene might be reactive. Accordingly experiments to condense guaiazulenium chloride, LIV, with aldehydes were carried out.

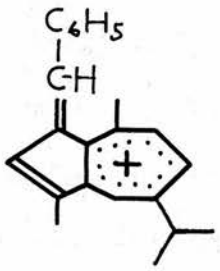
A solution of guaiazulene in methylene dichloride was saturated with hydrogen chloride and more than the equivalent quantity of benzaldehyde in the same solvent was added. The immediate result was the formation of a crystalline orange solid, benzylidene-guaiazulenium chloride, LXXXI, which proved to be unstable and could not be recrystallised. The analyses gave a lower value for carbon and a higher one for chlorine than those calculated. This was thought to be due to occlusion of hydrogen chloride. In subsequent experiments, guaiazulene and the aldehyde were dissolved in dry ether and then hydrogen chloride passed in. The solution went directly from blue to a suspension of the orange chloride, the supernatant losing most of its colour. It must be presumed that, in contrast to methylene dichloride, in ether as solvent the position of equilibrium lies largely towards guaiazulene and that it is only displaced to the cation by the reaction with the aldehyde. All the guaiazulene was used up, and it was found that the condensation occurred between molar quantities of each reactant. The benzylidene-guaiazulenium

chloride was dissolved in glacial acetic acid in which it was relatively stable. Addition of a saturated aqueous solution of picric acid then precipitated an orange picrate whose analysis corresponded to the salt involving the benzylidene-guaiazulenium cation. Attempted recrystallisation from glacial acetic acid was unsuccessful. Above 50°C., the solution decomposed to a green colour and removal of the solvent by distillation at lower temperature left a dark sticky solid.

The benzylidene-guaiazulenium chloride was hydrolysed slowly in aqueous solution and rapidly in alkali to a blue unstable compound, presumably the 'pseudo' base, LXXXIV. The state of division and therefore ease of isolation differed in a number of experiments. Acidification of the 'pseudo' base immediately after its formation caused it to form a yellow solution which might be the chloride, but this should be compared with the action of dilute acid on the hydrocarbons produced by the action of bases on the benzylidene-guaiazulenium salts (see later pages).



LXXXIV



LXXXI

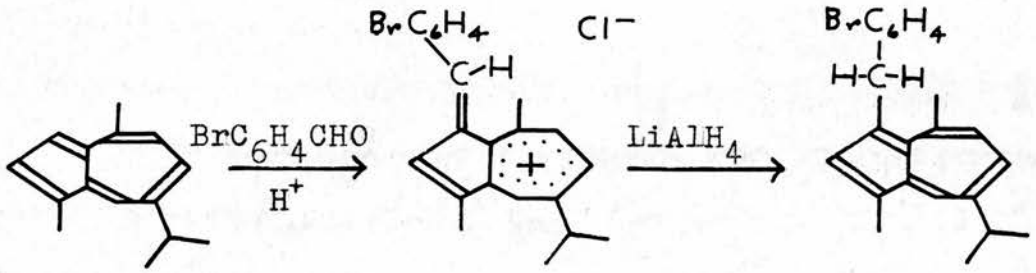
Green products which could not from the spectrum be benzyl guaiazulene were obtained in the reduction of benzylidene-guaiazulenium chloride with zinc amalgam and acetic acid. However, when a solution of the 'pseudo' base in 20% ethanolic hydrochloric acid was hydrogenated, the product was a blue green hydrocarbon, with position of maximum absorption, 630-35mμ, corresponding to that expected for a 3-alkyl-substituted-guaiazulene. The analysis, however, did not give good agreement for benzyl guaiazulene. Since the product of the reaction of guaiazulene with benzyl chloride (p.89) had almost the same analysis, but quite a different m.p., it must be concluded that the significance of the analysis of these hydrocarbons in determination of structure is limited. The two compounds differed in that the reduction product extracted into dilute hydrochloric acid. The other compound may well be diguaiazulyl ethane as suggested. This would be expected to have the absorption maximum in the same position.

A hydrogenation experiment was carried out on benzylidene-guaiazulenium chloride in AR acetic acid as solvent. The uptake of hydrogen was approximately mole per mole, but the product, although of almost the same analysis as that prepared from the 'pseudo' base, did not crystallise. An unstable product of the same properties was also obtained in an

experiment using ethanol saturated with sodium acetate as solvent. Neither formed a T.N.B. complex, c.f. benzoyl guaiazulene. Experiments on benzylidene-guaiazulenium-chloride and related compounds containing substituents in the phenyl group could not be performed in a precise quantitative manner as the material decomposed extensively during drying. It was therefore used immediately on formation after washing with ether and therefore contained considerable quantities of ether and hydrogen chloride.

Reaction of benzylidene-guaiazulenium chloride with lithium aluminium hydride produced a blue reduction product which behaved on chromatography as a hydrocarbon. It did not crystallise and gave a poor analysis for benzyl guaiazulene. This may be because these guaiazulene derivatives appear to have a tendency to oxidise which can occur much more readily when they are in the liquid state due to the readier diffusion of oxygen. It was therefore decided to use an aromatic aldehyde containing a substituent which could be estimated by analysis. m-Bromo-benzaldehyde was chosen and the orange chloride formed. It became partially hydrolysed in glacial acetic acid solution, so formic acid was used as solvent for picrate formation. The m-bromo-benzylidene-guaiazulenium chloride was reduced using lithium aluminium hydride to a blue crystalline product which gave a good analysis for

m-bromo-benzyl-guaiazulene, LXXXVI. The molecular weight determined by X-ray methods corresponded to this. The compound did not form a T.N.B. complex in common with other 3-alkyl-azulenes. The m-bromo-benzylidene-guaiazulenium salt with major contributant the fulvenoid form, LXXXV, and therefore red colour, was thus converted to a blue hydrocarbon with greater 'azulenic' resonance contributions, i.e.



III (λmax.605mμ) LXXXV (452mμ) LXXXVI (620mμ)

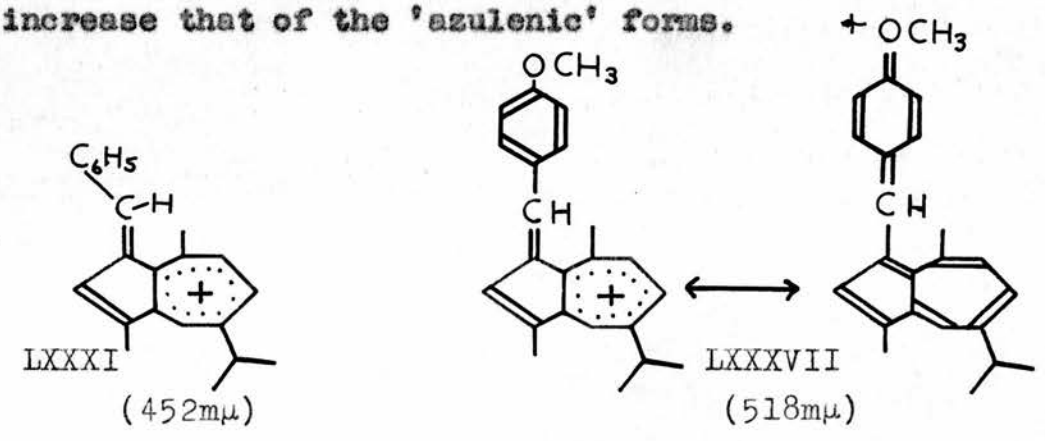
From the ionic nature of the chlorine and the colour of the aldehyde condensation products with guaiazulene and also the fact that they can be reduced to benzyl guaiazulenes with the corresponding absorption maximum it may be concluded that the formulation which has been given, e.g. LXXXV from m-bromo-benzaldehyde, is correct.

The effect on the spectrum of benzylidene-guaiazulenium chloride of electron donating substituents in the phenyl group was next examined. o- And p-methoxy-benzaldehydes,

piperonal and dimethylaminobenzaldehyde were used. These all gave red or orange crystalline chlorides when the method described for benzaldehyde was employed. The positions of the first absorption maxima of their cations in glacial acetic acid solution are tabulated below.

Cation	λ max. mμ.
benzylidene-guaiazulenium	452
m-Br- " "	452
o-MeO- " "	496
p-MeO- " "	518
piperonylidene- "	530
p-dimethylaminobenzylidene-guaiazulenium (in dil. HCl)	445

The bathochromic shift produced by the electron donating substituents is as expected, since they tend to reduce the contribution to the resonance hybrid of the fulvenoid form, and increase that of the 'azulenic' forms.



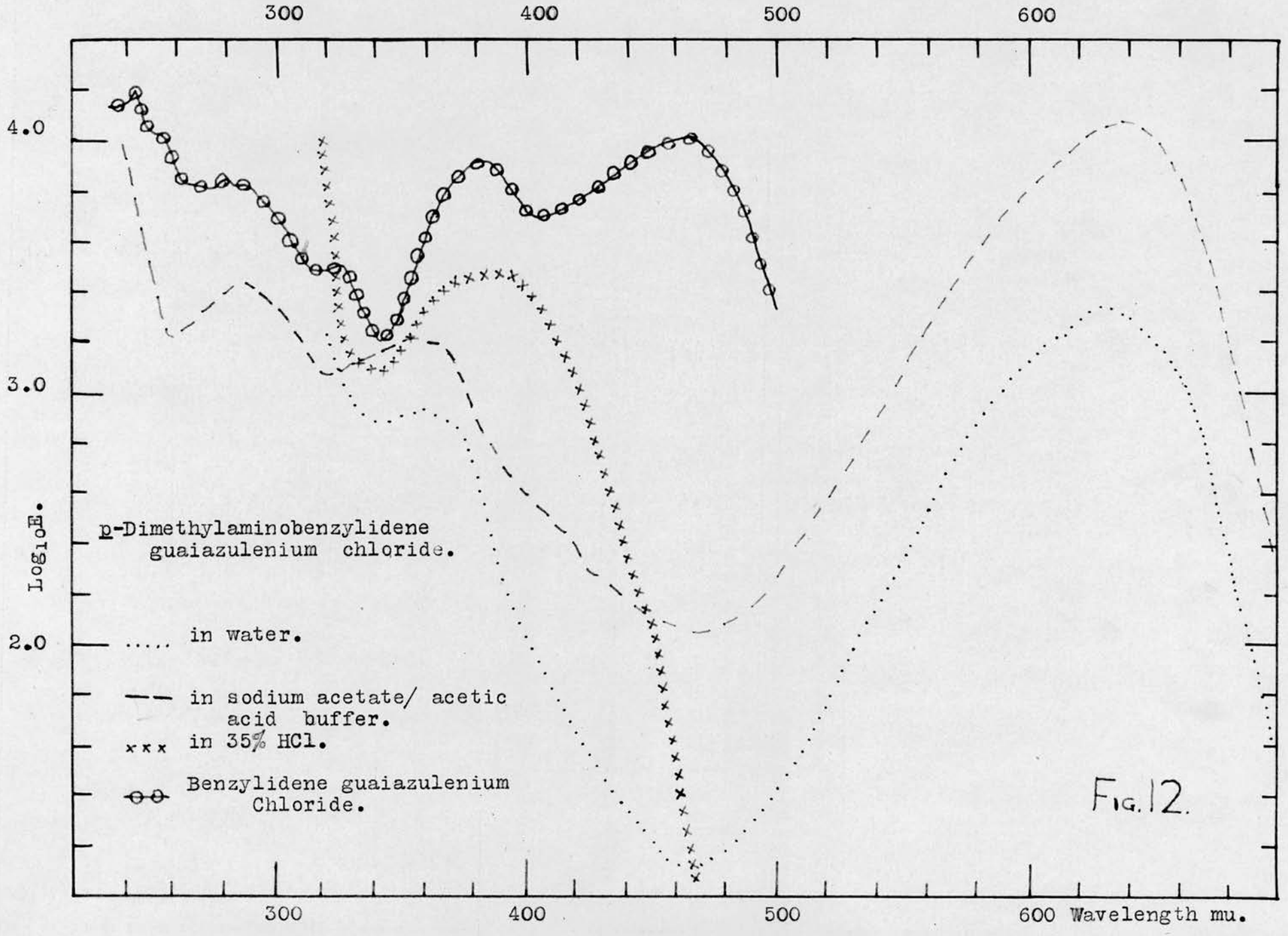
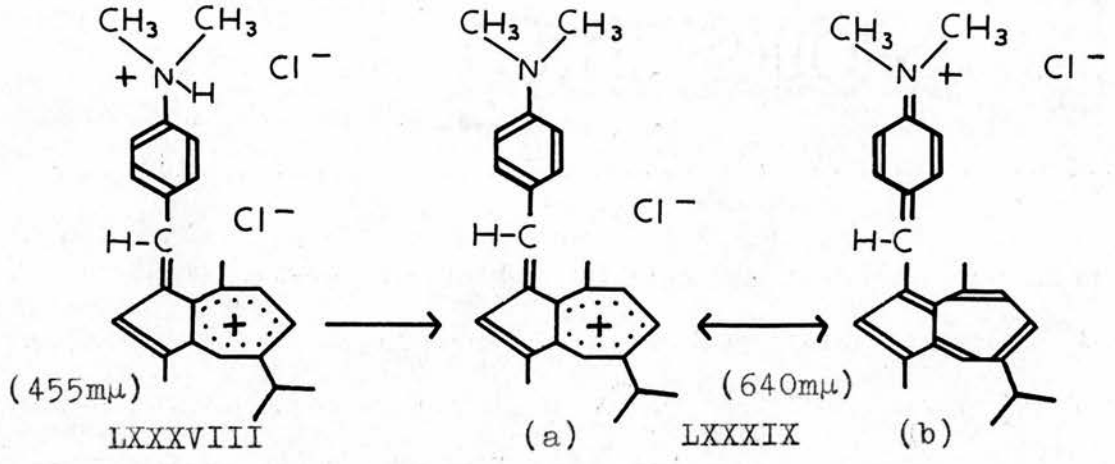

300
400
500
600
4.0
3.0
2.0
Log10E.
p-Dimethylaminobenzylidene guaiazulenium chloride.
..... in water.
—— in sodium acetate/ acetic acid buffer.
××× in 35% HCl.
Benzylidene guaiazulenium Chloride.
300
400
500
600 Wavelength mu.

Fig. 12.

In contrast a hypsochromic shift is found with p-dimethylaminobenzylidene-guaiazulenium chloride. This is due to the fact that it exists as a hydrochloride, LXXXVIII, with even greater contribution of the fulvenoid form than in the unsubstituted molecule. When the aqueous solution was buffered with sodium acetate, it became blue, λmax. 640mμ (fig.12) with a high visible absorption. It is presumed that it only now exists as the free p-dimethylaminobenzylidene-guaiazulenium mono-chloride, LXXXIX, with a marked bathochromic effect due to the strongly electron donating character of the p-dimethylamino group. This shift is equivalent to that of an alkyl substituent in the same position. Therefore LXXXIX(b) predominates.



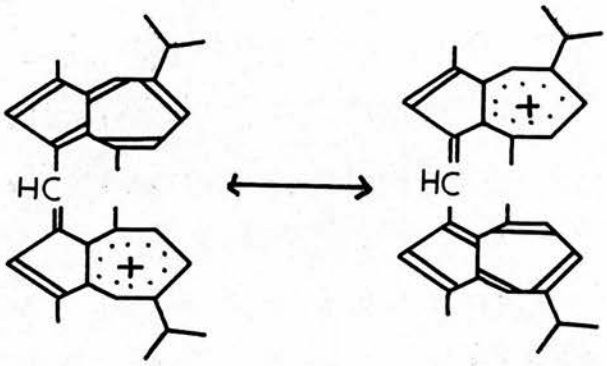
If for the condensation with guaiazulene in methylene dichloride instead of saturating a solution containing the free amino-aldehyde with hydrogen chloride, p-dimethylamino-

benzaldehyde hydrochloride was used, a solution was formed from which the blue mono-chloride was precipitated by addition of ether. Hydrogenation of this compound was attempted in glacial acetic acid solution, but there was very low hydrogen uptake and the solution decomposed in two days.

In a second attempt to prepare p-dimethylaminobenzylidene-guaiazulenium chloride in methylene dichloride by the same method, a yellow solution was formed which turned green on standing. No solid was precipitated by addition of ether. When poured into water it formed a blue solution which gave a green picrate. The ether layer contained in addition to guaiazulene, a blue/green hydrocarbon, max. 630mμ. thought to be dimethylaminophenyl diguaiazulyl methane, but the analysis was not good. This may be compared with a hydrocarbon obtained from a solution of benzylidene-guaiazulenium chloride left overnight in 20% hydrochloric acid. Its analysis corresponded fairly well to that of phenyl diguaiazulyl methane.

These condensation products from guaiazulene and acetaldehyde or cinnamaldehyde were not crystalline and were not further examined. That from guaiazulene-3-aldehyde was extremely unstable, but it was blue in colour corresponding

to the state:



LXXXIII B

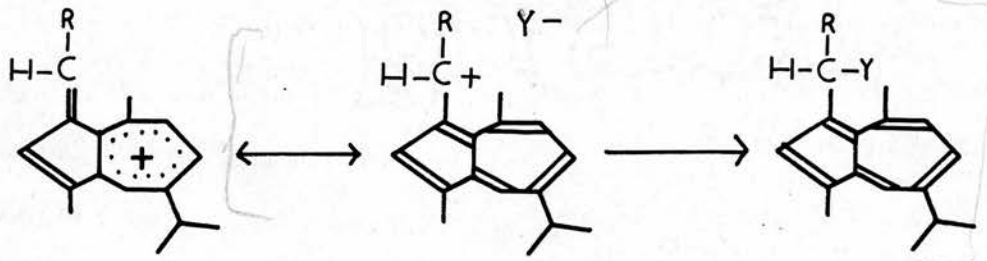
in which one of the guaiazulene nuclei remains 'azulenic'.

Since the hydrochlorides of the carbonyl compounds examined in section A are hydroxy derivatives of the corresponding methylene guaiazulenium chloride, this is comparable to the hydrochloride of diguaiazulyl ketone (p.88), and benzylidene guaiazulenium chloride to that of benzoyl guaiazulene (p.104).

The analysis of the guaiazulenium chloride had the low carbon and high chlorine values found in the benzylidene-guaiazulenium chlorides due to occlusion of hydrogen chloride. Using the conditions described above for the condensation of guaiazulene with piperonal, it was sometimes found that the product was not the red piperonylidene-guaiazulenium chloride, but a substance which crystallised in yellow/green shining needles which crushed to a red powder. It was insoluble in ether, but dissolved in ethanol, concentrated hydrochloric acid and to a small extent in water giving a red solution. Addition

of ether to a red solution in acetone changed the colour to blue. It reverted to red on acidification but was decolourised when neutralised with alkali. The picrate was red and had the m.p. and analysis of piperonylidene-guaiazulenium picrate. It was therefore assumed that the piperonylidene-guaiazulenium cation must be present in the green compound, and indeed its analysis corresponds to that of a complex of piperonylidene-guaiazulenium chloride with piperonal and hydrogen chloride.

The remainder of this section deals with a study of the attack by nucleophilic reagents on benzylidene-guaiazulenium chlorides. This might be supposed to occur by the simple mechanism.



XC	R=C_6H_4Br	Y=H
XCI	C_6H_5	CH_3
XCII	C_6H_4Br	CH_3
XCIII	C_6H_4Br	C_6H_5
XCIV	$C_7H_5O_2$	CH_3
XCV	C_6H_5	$CH(COC_6H_5)_2$

With each one, it was found that the solution turned from red to blue, indicating that an 'azulenic' system had been formed. In many of the reactions, a considerable quantity of the benzylidene-guaiazulenium chloride remained unreacted, and the yields were often very low.

As already stated, the product of the reaction of m-bromo-benzylidene-guaiazulenium chloride with lithium aluminium hydride was a blue crystalline solid, whose analysis and molecular weight corresponded to those of monomeric m-bromo-benzyl-guaiazulene, XC. It did not extract as a yellow solution into dilute hydrochloric acid unlike all the other hydrocarbons examined in this section. The unsubstituted benzylidene-guaiazulenium chloride on the other hand under the same conditions gave a hydrocarbon which would not crystallise. It had a poor analysis for benzyl guaiazulene and in common with other oils in this series probably oxidised very rapidly, the values for carbon content being almost invariably low. It did not extract into dilute hydrochloric acid, but no further evidence as to its structure is available.

The products from the reaction of m-bromo-benzylidene-guaiazulenium chloride with methyl magnesium iodide and phenyl magnesium bromide did not crystallise, but from their bromine content, the molecular weights were calculated assuming one atom of bromine in the molecule. The values corresponded

approximately to that for $BrC_6H_4CH+\underline{Gu}^3 + CH_3$ or C_6H_5. On this assumption, the analysis figures for carbon and hydrogen compared with those of XCII and XCIII were fairly good, considering that the crude liquids were used. The values for bromine were rather low. Using methyl magnesium iodide with benzylidene-guaiazulenium chloride, and piperonylidene-guaiazulenium chloride, the analyses were reasonable for the corresponding compounds, XCI and XCIV, but the only hydrocarbon fraction from the reaction of phenyl magnesium bromide with benzylidene-guaiazulenium chloride was deposited as crystals in 0.2% yield after solvating the impurity by association with T.N.B. It was thought at first to be the expected diphenyl guaiazulyl methane, but the molecular weight derived by X-ray methods corresponded very closely to that of phenyl diguaiazulyl methane.

In the reactions of these salts with lithium aluminium hydride or Grignard reagents, the attack is as expected, by addition to the positively charged carbon atom α to carbon-3 of guaiazulene. The product of the reaction of phenyl magnesium bromide with benzylidene-guaiazulenium chloride in minute yield appears to be exceptional.

Because of the uncertain nature of the blue products derived by the action of dilute sodium hydroxide on the benzylidene-guaiazulenium chlorides, it was decided to use

potassium ethoxide dissolved in a non-hydroxylic solvent, dry benzene. The reactions with benzylidene-guaiazulenium chloride and piperonylidene- and anisylidene-guaiazulenium chlorides all gave products whose analysis corresponded to one oxygen atom too few for the α-ethoxy-3-benzylguaiazulene. With the m-bromo-benzylidene salt the molecular weight was calculated to be about 545 assuming one bromine atom per molecule. This is approximately that of BrC_6H_4CH + 2Gu. For such a structure the bromine content is rather low. However it is our experience that bromine analyses are on the average low. The reaction with potassium ethoxide in ethanol on benzylidene-guaiazulenium chloride gave a product whose analysis was almost the same as that obtained with benzene as solvent. The m.p. of these hydrocarbons were so variable as to be useless for purposes of comparison. There appeared to be no polymerisation, but rather direct attack in the reaction of dibenzoyl methane with benzylidene-guaiazulenium chloride in presence of potassium ethoxide. The analysis corresponded well to the structure XCV.

Since the polymerisation reactions appeared to be base catalysed, it was decided to react the benzylidene-guaiazulenium salts with amines. The product from benzylidene-guaiazulenium chloride with aniline had a very low nitrogen content. It was not certain whether this was a real value, so p-chloraniline was used to introduce a chlorine 'label' whose analysis might be

more significant. This product contained no chlorine or nitrogen, therefore it was presumed that the figure for nitrogen previously mentioned was spurious. The two compounds were probably identical and had a different appearance from the hydrocarbon derived from the reaction with potassium ethoxide. Reaction of m-bromo-benzylidene-guaiazulenium chloride with aniline also gave a product whose analysis showed a very small quantity of nitrogen. From the assumption of one atom of bromine per molecule, the molecular weight was calculated to be about 788 which is equivalent to $BrC_6H_4CH + 3\underline{Gu} + C_2H_4$. On this basis the analyses for this compound and its analogue containing no bromine were not very good. A colour change to blue or green was also observed on addition of ammonia trimethylamine or pyridine to benzylidene-guaiazulenium chlorides. The products did not crystallise and their analyses all showed a small figure for nitrogen. Extraction into dilute hydrochloric acid giving a yellow solution was observed in each case.

Finally potassium cyanide was used as a nucleophilic reagent. The products from benzylidene-guaiazulenium chloride under anhydrous conditions were guaiazulene, a hydrocarbon and a nitrile. The analysis of the latter corresponded to that of α-phenyl-3-α-guaiazulyl-acetonitrile, but the structure of the hydrocarbon was not immediately obvious. With aqueous

conditions, the yield of the nitrile was increased, but the hydrocarbon and guaiazulene were produced in much lower quantity. The results were of the same order with m-bromobenzylidene-guaiazulenium chloride. In this case, assuming one atom of bromine per molecule, there were two cyano groups and the molecular weight corresponded to BrC_6H_4CH + 2Gu + C_2H_2 + 2CN and for the hydrocarbon, BrC_6H_4CH + 3Gu + CH.

Light was shed on the structure of the nitriles by examination of the ketones derived from them by alkaline oxidation in presence of air. (c.f. Oxidation of α-cyanobenzyl benzanthrone, MacGregor: Ph.D. Thesis, Edinburgh, 1941). The product from the benzylidene salt was the already known benzoyl guaiazulene (section A, p. 81) confirmed by a molecular weight determination. However the bromine-containing nitrile gave a diketone (from the calculated molecular weight) which in acid resembles the hydrochloride of benzoyl guaiazulene rather than that of diguaiazulyl ketone. This provided evidence that neither of the carbonyl groups is attached to the three position of two guaiazulene nuclei. The overall position is then:

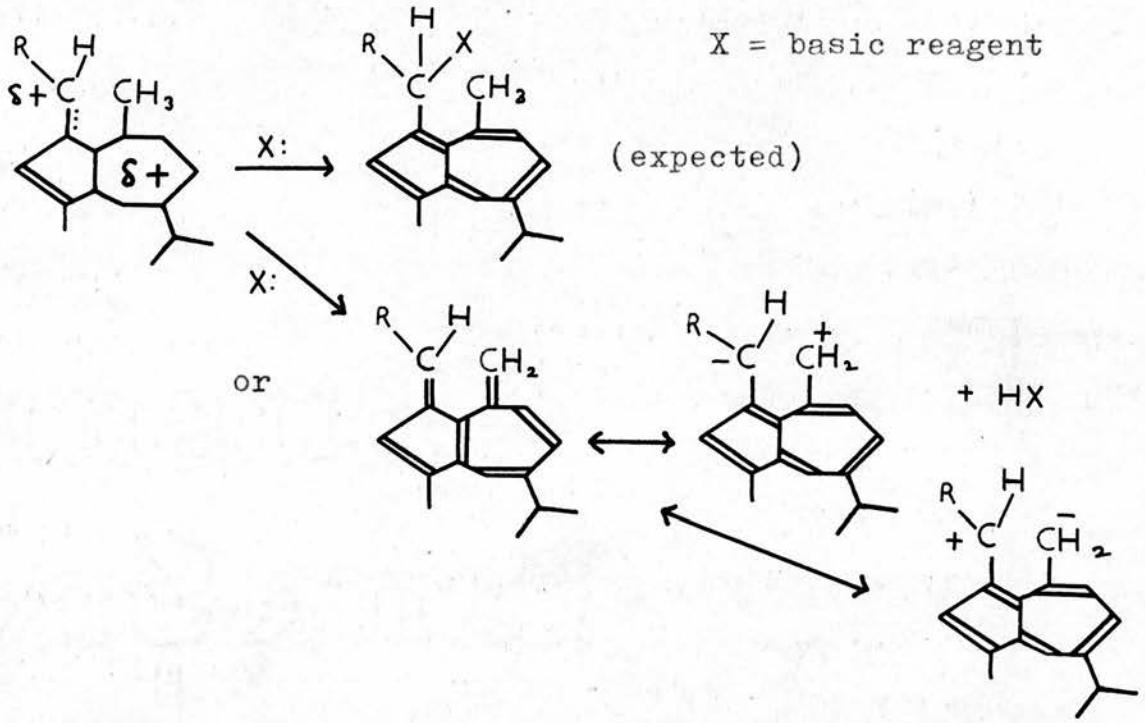
$$2[C_{22}H_{22}Br]^+ \xrightarrow{2CN^-} \begin{array}{llll} C_{46} & H_{44} & N_2 & Br_2 \\ C_{40} & H_{39} & N_2 & Br \\ \hline C_6 & H_5 & & Br \end{array}$$

with one molecule of bromobenzene lost in condensation of two

molecules of the salt. This process seems to be preferred under aqueous conditions, but in the reactions producing a greater proportion of hydrocarbon, the accompanying guaiazulene may be significant in determining the mechanism of this alternative reaction. The product of the reaction of cyanide on o-methoxy-benzylidene-guaiazulenium chloride was the simple o-methoxy-phenyl-guaiazulyl acetonitrile which required passage of air to bring about alkaline hydrolysis. That from p-nitro-benzylidene-guaiazulenium chloride contained two nitro-benzylidene and three guaiazulene units. A derived ketone also appeared to be present. It seems that the presence of an electron attracting substituent in the phenyl group of the nitriles adds to the ease of alkaline hydrolysis.

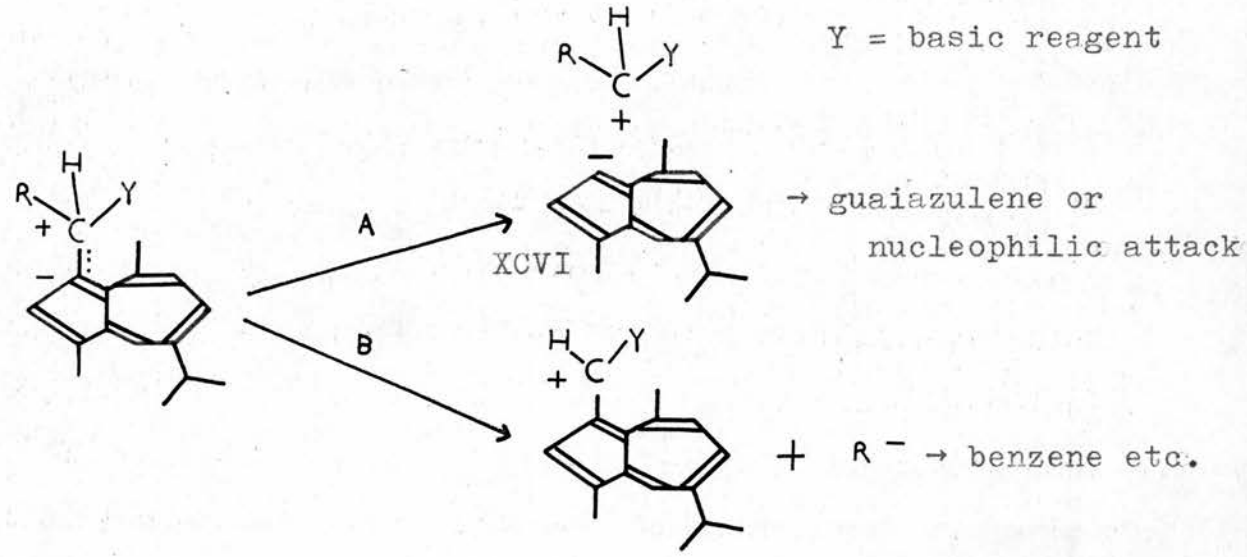
All these reactions have one thing in common - they involve the attack of a base on the benzylidene-guaiazulenium salt. A nucleophilic attack occurs in the expected manner only in the case of the lithium aluminium hydride reduction and the Grignard reaction. Ethoxide, amines and cyanide react anomalously, although it is apparent that each reproducibly gives the same product or products in repeated experiments. The reaction must consequently be dependent on the character of the base. The comparison of the nitriles obtained from the bromobenzylidene and the benzylidene compounds indicates that at least for the reaction with

cyanide ion the nature of the product is also extremely dependent on the nature of the phenyl residue. The question now arises as to the possible alternative modes of attack of a base on the benzylidene-guaiazulenium salts.



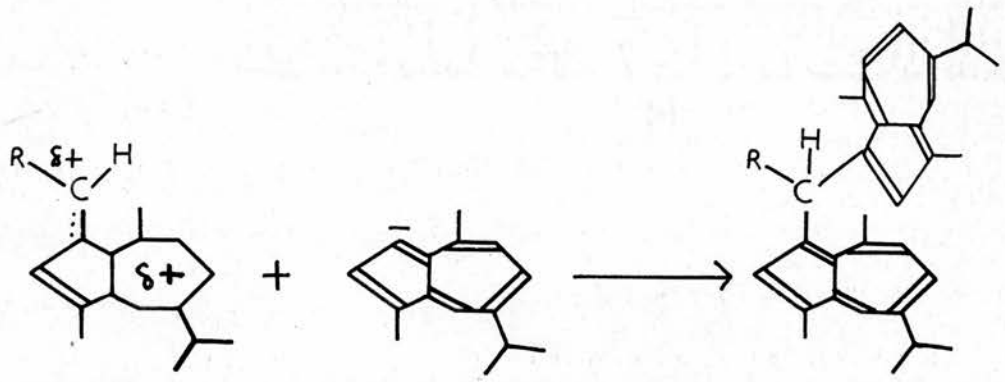
The expected mechanism involving addition is obviously only sufficient for the Grignard-type reaction and for the attack of cyanide ion to give the nitrile in the benzylidene compound but not in the bromobenzylidene compound. The alternative mechanism involved removal of a hydrogen ion. These two mechanisms must both be employed to explain the variety of products obtained.

The product of base-addition might decompose in two ways,

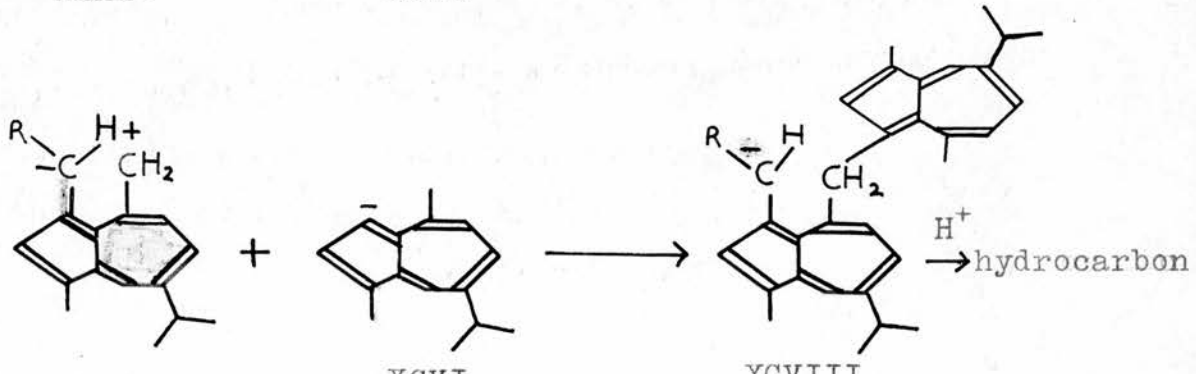


XCVII

The method A would explain the formation of the hydrocarbons thus:

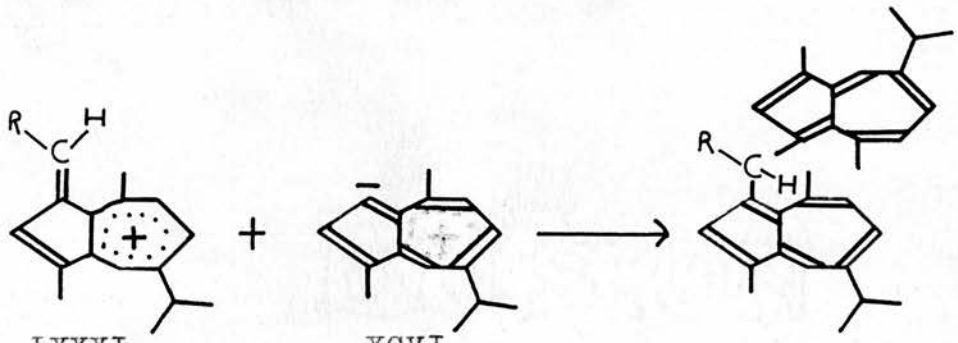


LXXXI XCVI



XCVI XCVIII

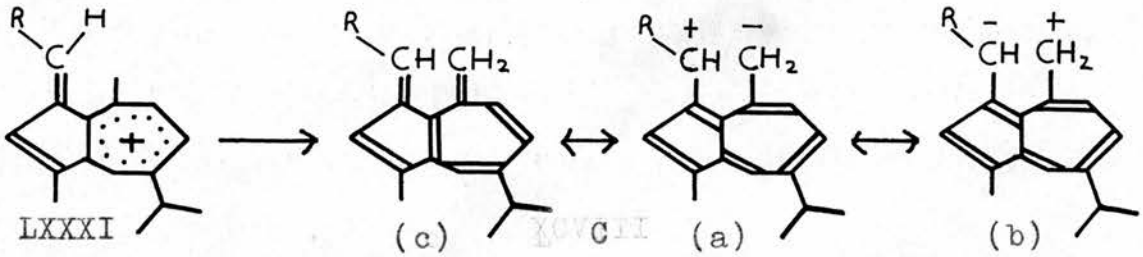
The ion, XCVIII, might then break down by oxidation with loss of R^- to yield products with an increase in guaiazulene residue content. The method B, although it appears the most probable, seems only to operate in the bromo-benzylidene/cyanide reaction giving the nitrile. The question now arises as to the method of attack of these two ions, XCVI and XCVII. The most apparent is



LXXXI XCVI

This is not however sufficient to explain the multiplicity of products, especially those involving three guaiazulene units.

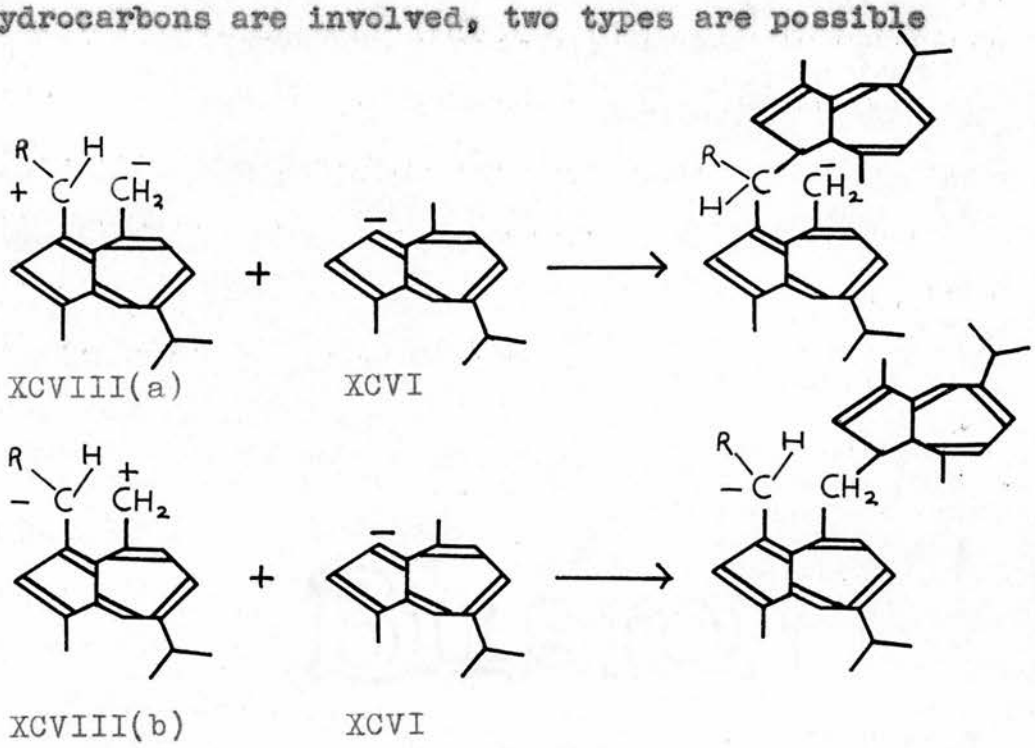
The alternative mode of attack by a base is regarded as involving the removal of a proton



LXXXI (c) XCVII (a) (b)

from the 4-methyl group. The isopropyl is sterically less likely and the 4-position is a centre of nucleophilic attack

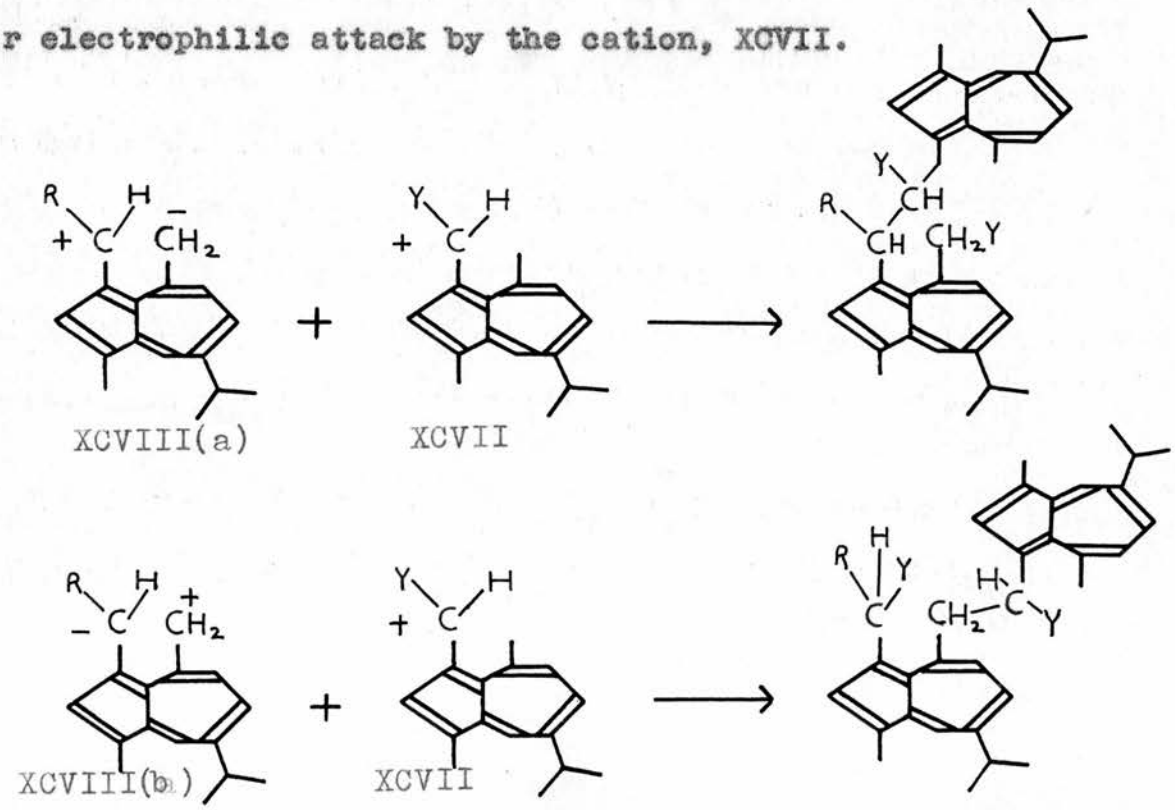
in azulene (c.f. the reactivity of α-picoline methiodide). When hydrocarbons are involved, two types are possible



XCVIII(a) XCVI

XCVIII(b) XCVI

each of which would subsequently add a proton. Similarly for electrophilic attack by the cation, XCVII.

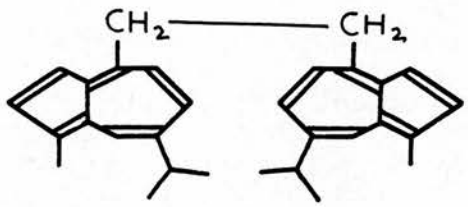


XCVIII(a) XCVII

XCVIII(b) XCVII

It appears that the latter is the only satisfactory formulation for the dinitrile from bromo-benzylidene-guaiazulenium chloride if the derived diketone is to have the same colour in acid as benzoyl guaiazulene. From this it may be concluded that the former is more probable for hydrocarbon formation, but both methods may apply.

One of the products of the reaction of guaiazulene with sodamide is a dimer with the same absorption spectrum as guaiazulene. It is concluded to be a condensation product linked through one of the alkyl groups by oxidation, e.g. XCIX . The addition to the hydrocarbons containing two guaiazulene residues of a third guaiazulene unit may occur by this means.



XCIX

The absorption spectra of these compounds were all determined. The curves were practically coincidental for all the hydrocarbons and nitriles derived by the reaction of bases on the salts. They were extremely similar to that of the m-bromobenzyl compound, (fig.13), indicating that each

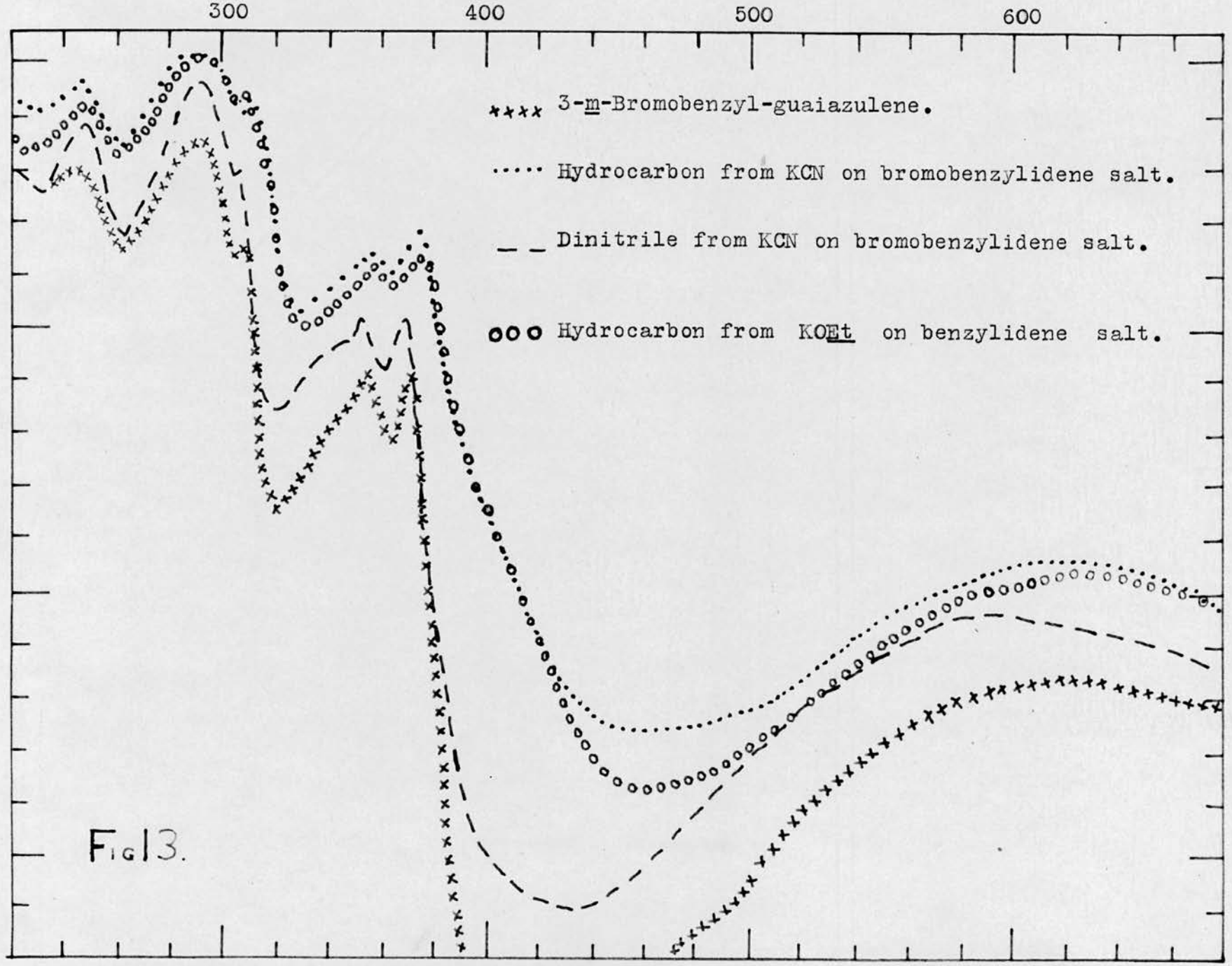

300
400
500
600
5.0
4.0
3.0
2.0
Log10E.
**** 3-m-Bromobenzyl-guaiazulene.
····· Hydrocarbon from KCN on bromobenzylidene salt.
_ _ Dinitrile from KCN on bromobenzylidene salt.
ooo Hydrocarbon from KOEt on benzylidene salt.

Fig 13.

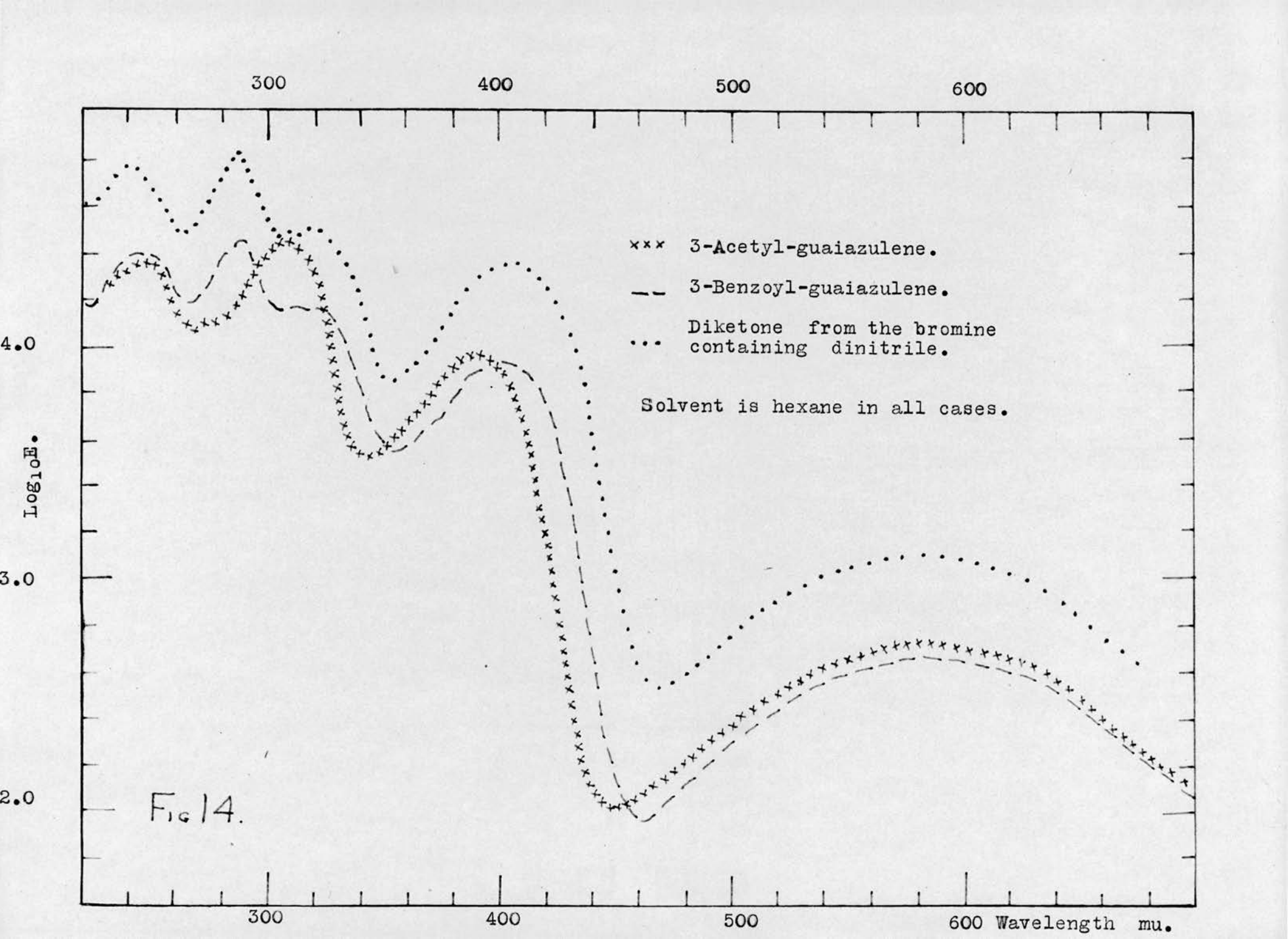

300
400
500
600
4.0
3.0
2.0
Log10E.
××× 3-Acetyl-guaiazulene.
__ 3-Benzoyl-guaiazulene.
... Diketone from the bromine containing dinitrile.
Solvent is hexane in all cases.
300
400
500
600 Wavelength mu.

Fig 14.

guaiazulene nucleus involved in the complex structures probably bears a 3-alkyl substituent. The diketone has a curve similar to the benzoyl compound with of course enhanced ε values, (fig.14), indicative of the summation of the two acyl azulene residues present.

The formation of these benzylidene-guaiazulenium salts is indicative of the presence in the guaiazulenium cation of a reactive methylene group. The ability of the 3-α-carbon atom in the resulting salts to suffer nucleophilic attack is apparent, but it appears likely that in addition the attack of bases on these salts can, as an alternative, remove a proton. As this is a similar process to the action of sodamide on guaiazulene which leads to a dimer, the multiplicity of types of product may be explained.

E X P E R I M E N T A L

EXPERIMENTAL

Condensation of guaiazulene with benzaldehyde.

A solution of guaiazulene (1 g.) in dry ether (150 ml.) containing benzaldehyde (0.9 g.) was saturated with hydrogen chloride. A micro-crystalline orange solid which was rapidly formed was collected and washed with ether. It could not be recrystallised and did not melt sharply. The conversion was almost quantitative, but analysis showed that extensive decomposition rapidly occurred. The material was dissolved in glacial acetic acid and four times its volume of a saturated aqueous solution of picric acid was slowly added. Orange crystals of a picrate separated which could not be recrystallised from glacial acetic acid since warming the solution above 50°C. caused decomposition to a green solution, and removal of the solvent by distillation at a lower temperature left a dark sticky solid. The m.p. of the crude picrate was 101-102.5°C. (Found: C,65.7; H, 5.1; N, 8.1. Benzylidene-guaiazulenium picrate, $C_{28}H_{26}N_3O_7$, requires C,65.2; H, 5.0; N, 8.1%).

When a solution of benzylidene-guaiazulenium chloride in 20% aqueous hydrochloric acid was kept overnight, a blue solid separated. It was extracted into ether which was then removed by distillation. The residue was recrystallised twice

from ethanol and then from ethyl acetate. M.p. 170-174°C. (Found: C, 91.2; H, 8.2. Phenyl+2Cu^3 + CH , $C_{37}H_{40}$, requires C, 91.7; H, 8.3%).

The condensation of guaiazulene (462 mg.) and benzaldehyde (372 mg.) was repeated and the ether suspension of benzylidene-guaiazulenium chloride poured into water. The blue ether phase was separated, and the aqueous phase was washed with petrol ether until the washings were colourless. The red aqueous layer was then made alkaline by addition of 10% aqueous sodium hydroxide solution. In one experiment the resulting blue suspension of the 'pseudo' base was extracted with ether and the extract concentrated by distillation. Addition of ethanol then caused a white/green solid to separate. It decomposed to a brown material at about 200°C. Addition of dilute hydrochloric acid converted the solid to a yellow solution. In a second experiment using the same proportions of reactants, addition of alkali to the red salt solution precipitated an unstable blue/green solid which was washed with water and ethanol. Yield: 616 mg., c.80%. This solid was dissolved in 20% ethanolic hydrochloric acid and hydrogenated at atmospheric pressure for 3 hours using Adam's catalyst. The colour of the solution changed from orange to brown. It was extracted with ether and then with chloroform leaving a colourless solution. The extracts were prepared

for chromatography in the normal way. The hydrocarbon fraction (petrol ether) had λmax.630-35mμ. It was recrystallised from the minimum quantity of petrol ether after the addition of ethanol. M.p. 154-154.5°C. Yield: 113 mg.,c.20%. (Found: C, 90.4; H, 8.3. Benzyl - guaiazulene, $C_{22}H_{24}$, requires C, 91.6; H, 8.40%). The extract in chloroform was taken to dryness and the residue extracted with ethanol. The same hydrocarbon went into solution leaving a tar.

Further hydrogenation experiments were carried out on the orange benzylidene-guaiazulenium chloride rather than on the 'pseudo' base. Since it decomposed during drying it was used immediately on formation after only washing with ether. It was thus impossible to carry out experiments in a precise quantitative manner as the material contained considerable quantities of ether and HCl. The chloride was dissolved in AR acetic acid and hydrogenated at atmospheric pressure using Adam's catalyst. After 18 minutes, 165 ml. of hydrogen was taken up. The calculated value assuming uptake to be mole per mole is about this volume. The solution was mixed with ether and extracted five times with water which removed a small quantity of unchanged benzylidene-guaiazulenium chloride. The material in the extract chromatographed as a hydrocarbon but did not crystallise or form a T.N.B. complex. (Found: C, 90.1; H, 8.7%). It decomposed within a few days.

Condensation of guaiazulene with p-dimethylaminobenzaldehyde.

The method used above for benzaldehyde (1 mole of guaiazulene to 1.5 moles of aldehyde) gave an orange salt, but when p-dimethylaminobenzaldehyde hydrochloride (1 mole) was added to a solution of guaiazulene (2 moles) in methylene dichloride as solvent, a yellow solution was formed which became green. It was poured into water, and after extraction with ether to remove guaiazulene, a saturated aqueous solution of picric acid was added. The resulting green picrate decomposed at about 100°C. Chromatography of the material in the ether extract separated a blue/green fraction (benzene), λmax.630-35mμ. The compound was recrystallised from ethanol and then ethyl acetate, m.p. 191-193°C. (Found: C, 84.8; H, 8.3; N, 2.3. p-Dimethylaminophenyl+2Gu^3 + CH, $C_{39}H_{45}N$, requires C, 88.8; H, 8.5; N, 2.7%). It formed a brown picrate which melted to a blue liquid at 152-152.5°C. In a second experiment, addition of ether to the reaction mixture in methylene dichloride precipitated the mono-hydrochloride as an unstable blue/green solid, m.p. 144-145°C., in c.20% yield.

Condensation of guaiazulene with other aldehydes.

The method described for benzaldehyde (1 mole of guaiazulene to 1.5 moles of aldehyde) was employed.

With acetaldehyde the product was a dark red sticky solid. Using cinnimaldehyde, it was a red paste which formed a bright red aqueous solution. Addition of alkali converted it to an unstable green 'pseudo' base. Micro-crystalline solids were however obtained from anisaldehyde, o-methoxy-benzaldehyde and piperonal. They were converted in glacial acetic acid solution to picrates by the method described above.

Anisaldehyde formed a plum coloured p-methoxy-benzylidene-guaiazulenium chloride and a red/brown picrate, m.p. c.150°C. (dec.). (Found: C, 64.7; H, 5.2; N, 8.4. $C_{29}H_{27}N_3O_8$ requires C, 63.8; H, 5.0; N, 7.7%).

o-Methoxy-benzaldehyde formed an orange/red chloride and an orange picrate, m.p. 103-106°C. (dec.). (Found: C, 64.4; H, 5.2; N, 6.8. $C_{29}H_{27}N_3O_8$ requires C, 63.8; H, 5.0; N, 7.7%).

Piperonal formed a red chloride and a red picrate, m.p. 104-105°C.(dec.). (Found: C, 62.7; H, 4.6; N, 6.9. $C_{29}H_{25}N_3O_8$ requires C, 62.2; H, 4.5; N, 7.5%). In some experiments under apparently the same conditions, in place of the red piperonylidene-guaiazulenium chloride, yellow/green shining needles were obtained. They were insoluble in ether, but dissolved in ethanol, concentrated hydrochloric acid and to some extent in water giving bright red solutions. Addition of ether to a red acetone solution changed the colour to blue. Acidification made it revert to red and it became colourless

on addition of alkali. (Found: C, 66.9, 66.2, 67.5; H, 6.2, 6.1, 6.6; N, nil; Cl,--,14.5,11.6%). It formed a red picrate, m.p. 108°C. (dec.). (Found: C, 61.9; H, 4.3; N, 7.8%), i.e. the same picrate is formed. A complex of piperonylidene-guaiazulenium chloride with piperonal and hydrogen chloride, $C_{31}H_{30}O_5Cl_2$, requires C, 67.2; H, 5.4; Cl, 12.8%.

Guaiazulene-3-aldehyde: the reaction produced a blue solid.

Reduction of benzylidene-guaiazulenium chloride.

Lithium aluminium hydride (0.5 g.) was suspended in dry ether (25 ml.) and the benzylidene-guaiazulenium chloride prepared from 2 g. guaiazulene added. Heat was immediately evolved and the solution turned blue. After 10 minutes the complex was decomposed by addition of water and the solution, after filtration to remove unchanged material, was extracted with ether. The extract was treated normally. The material chromatographed was completely eluted by petrol ether except for a narrow yellow strongly adsorbed band. The hydrocarbon did not crystallise even after distillation at 0.5 mm. pressure. Yield of blue oil: 0.97 g., c.50%.

Condensation of guaiazulene with m-bromo-benzaldehyde.

A solution of guaiazulene (1.46 g.) in dry ether (40 ml.) containing m-bromo-benzaldehyde (2.04 g.) was saturated with hydrogen chloride. The orange precipitate which separated was collected and a small portion dissolved in formic acid. A saturated aqueous solution of picric acid was then slowly added until precipitation of the orange picrate was complete. M.p. 74-75°C. (dec.) (Found: C, 56.6; H, 4.3; N, 7.0; Br, 12.4. $C_{28}H_{25}N_3O_7Br$ requires C, 56.6; H, 4.2; N, 7.1; Br, 13.5%).

Reduction of m-bromo-benzylidene-guaiazulenium chloride.

The major portion of the m-bromo-benzylidene-guaiazulenium chloride prepared in the experiment described above was added to dry ether containing a large excess of lithium aluminium hydride. There was a vigorous reaction and the solution turned blue. After 30 minutes, the complex was hydrolysed by addition of water and the ether layer separated. Chromatography showed that the only product was a hydrocarbon (petrol ether). It crystallised from ethanol in elongated blue plates, m.p. 77-78°C. (Found: C, 71.7; H, 6.5; Br, 21.9. Bromo-benzyl-guaiazulene, $C_{22}H_{23}Br$, requires C, 71.9; H, 6.3; Br, 21.8%). The volume of the unit cell of this compound was found by X-ray methods to be 934·7A^3. The observed density was 1.30 g./cc.

Therefore the molecular weight was calculated to be 732/n, where n = the number of molecules per unit cell. The molecular weight of m-bromo-benzyl-guaiazulene is 367. It may therefore be presumed that the compound is monomeric m-bromo-benzyl-guaiazulene with two molecules per unit cell. This is consistent with the X-ray evidence.

Reaction of benzylidene-guaiazulenium chlorides with methyl magnesium iodide.

A paste of the chloride was added to a solution of excess methyl magnesium iodide in dry ether. A vigorous reaction occurred in each case and the solution turned blue. It was boiled under reflux for 30 minutes and the complex was then decomposed by addition of a saturated aqueous solution of ammonium chloride. A considerable proportion of each of the red chloride remained unreacted, and this was filtered off before the ether phase was separated. It was prepared for chromatography in the normal way. With benzylidene-guaiazulenium chloride, the majority of the material was blue (petrol ether), λmax.630mμ. It did not crystallise and decomposed after a few days. (Found: C, 90.7; H, 9.1; α-phenyl-α-3-guaiazulyl-ethane, $C_{23}H_{26}$, requires, C, 91.4; H, 8.6%). The main product from the reaction using piperonylidene-guaiazulenium chloride was blue/green (petrol ether(1)/benzene(1)). It

distilled at 0.5 mm. pressure to a green liquid which had a slight tendency to crystallise. (Found: C, 82.5; H, 7.9. α-Piperonyl-α-3-guaiazulyl-ethane, $C_{24}H_{26}O_2$, requires C, 83.2; H, 7.6%). The fraction eluted by petrol ether from the reaction with m-bromo-benzylidene-guaiazulenium chloride was blue. It did not crystallise but formed a hard tar which decomposed after standing for several days. (Found: C, 71.8; H, 6.8; Br, 19.4. m-Bromo-phenyl-methyl-guaiazulyl-methane, $C_{23}H_{25}Br$, requires C, 72.4; H, 6.6; Br, 21.0%).

Reaction of benzylidene-guaiazulenium chloride with phenyl magnesium bromide.

The benzylidene-guaiazulenium chloride from 1 g. guaiazulene was suspended in dry benzene and added to a solution of excess phenyl magnesium bromide in dry ether. The solution became green and after 30 minutes it was poured into water. The ether layer was separated and treated in the normal way. A blue hydrocarbon fraction (petrol ether) was obtained which did not crystallise until it was boiled in ethanol solution with T.N.B. Then it formed blue lozenge shaped crystals, m.p. 179-182°C. Yield: 20 mg. (Found: C, 91.4; H, 8.1, N, nil. Diphenyl guaiazulyl methane, $C_{28}H_{28}$, requires C, 92.3; H, 7.8%). The crystals appeared to be orthorhombic and of cell volume 2919.8A^3. Since the density of the solid was measured as 1.10g./cc., the

molecular weight was calculated to be 1935/n. The nature of the crystal suggested that the value of n, the number of molecules in the unit cell, is four or less probably eight. Therefore the molecular weight could be 484 or 242. This does not correspond to the formula weight of diphenyl guaiazulyl methane but suggests instead diguaiazulyl phenyl methane which requires C, 91.7; H, 8.3%.

The same method was applied in the reaction of m-bromo-benzylidene-guaiazulenium chloride with phenyl magnesium bromide. The blue product (petrol ether) did not crystallise. Within a week it partially decomposed forming a hard tar. (Found: C, 76.3; H, 6.4; Br, 17.0. m-Bromophenyl-phenyl-3-guaiazulyl-methane, $C_{28}H_{27}Br$, requires C, 75.7; H, 6.1; Br, 18.1%).

Reaction of benzylidene-guaiazulenium chlorides with potassium ethoxide.

The benzylidene chloride prepared from the appropriate aldehyde and 1 g. guaiazulene was suspended in benzene (30 ml.) and excess of potassium ethoxide added. The mixture was kept at room temperature with occasional shaking for 24 hours. The resulting blue solution, filtered to remove a large quantity of unchanged benzylidene-guaiazulenium chloride, was taken to dryness, and the residue chromatographed in petrol ether solution.

Benzylidene-guaiazulenium chloride (from 1 g. guaiazulene) gave a blue band eluted (petrol ether(4)/benzene(1)) as a blue solution which crystallised on removal of the solvent. Rechromatography separated traces of guaiazulene and a green material from it. The other bands were of decomposition products. The blue solid had m.p. 155-158°C. Yield: 42 mg. (Found: C, 90.9; H, 8.1. $C_6H_5CH_2 + \underline{Gu}^{3\cdot4} + \underline{Gu}^{3}$, $C_{37}H_{40}$, requires C, 91.7; H, 8.3%).

m-Bromo-benzylidene-guaiazulenium chloride: about 2.5 g. of a paste of the chloride was used and the solution started to turn blue almost immediately after addition of the potassium ethoxide. Little unchanged m-bromo-benzylidene-guaiazulenium chloride remained after 18 hours. Chromatography separated guaiazulene, a blue fraction (petrol ether (2)/benzene(1)), green decomposition products and a bright blue band (ether(9)/ethanol(1)) which was the 'pseudo' base from hydrolysis of the starting material. The blue fraction crystallised from petrol ether/ethanol as a blue solid, m.p. c.190°C., variable with rate of heating. Yield: 115 mg. (Found: C, 79.1; H, 7.0; Br, 14.7. $BrC_6H_4CH_2 + \underline{Gu}^{3\cdot4} + \underline{Gu}^{3}$, $C_{37}H_{39}Br$, requires C, 78.8; H, 7.0: Br, 14.2%).

Piperonylidene-guaiazulenium chloride: The benzene solution first changed to purple and then to green. Chromatography separated guaiazulene and a number of green decomposition

products from a blue fraction (petrol ether(2)/benzene(1)). The solution crystallised, when concentrated and was then recrystallised from a mixture of benzene and ethanol and then from ethyl acetate, m.p. variable with rate of heating. (Found: C, 85.8; H, 7.4. $C_7H_5O_2CH_2$ + $\underline{Gu}^{3\cdot4}$ + $\underline{Gu}^{3}$, $C_{38}H_{40}O_2$, requires C, 86.3; H, 7.6%).

Anisylidene-guaiazulenium chloride: The benzene solution was again green and the mixture of products similar. A blue solid, recrystallised from ethyl acetate, was obtained, whose m.p. varied with the rate of heating. (Found: C, 88.0; H, 8.1. $CH_3O\cdot C_6H_4CH$ + 2$\underline{Gu}$, $C_{38}H_{42}O$, requires C, 88.7; H, 8.2%).

An experiment was carried out with 2 g. of a paste of benzylidene-guaiazulenium chloride suspended in dry ethanol (50 ml.) to which ethanol (25 ml.) containing sodium (0.3 g.) was added over 5 minutes. The solution turned blue/green and after 15 minutes it was neutralised by addition of 20% aqueous hydrochloric acid (50 ml.). The solution was extracted with ether but some of the coloured material remained in the aqueous phase.

The extract was prepared for chromatography in the usual manner. A blue material (petrol ether(1)/benzene(1)) was separated from small quantities of decomposition products. It decomposed further during rechromatography, but 535 mg. of a blue solid with no sharp m.p. was obtained. (Found: C, 89.9; H, 8.5. C_6H_5CH + 2$\underline{Gu}^{3}$. $C_{37}H_{40}$, requires C, 91.7, H, 8.3%).

Reaction of benzylidene-guaiazulenium chloride with dibenzoyl methane.

Benzylidene-guaiazulenium chloride was suspended in dry benzene and excess of dibenzoyl methane and potassium ethoxide added. The solution became green and after 18 hours was filtered to remove unchanged benzylidene-guaiazulenium chloride. Concentration of the solution caused crystallisation of colourless needles with green occluded material. Repeated recrystallisation from ethanol separated the green compound as needles, m.p. 171-172°C. (Found: C, 86.2; H, 6.7. Phenyl guaiazulyl dibenzoyl methane, $C_{37}H_{34}O_2$, requires C, 87.0, H, 6.7%).

Reaction of benzylidene-guaiazulenium chloride with potassium cyanide.

(a) Under aqueous conditions.

The benzylidene-guaiazulenium chloride from 1 g. guaiazulene was suspended in benzene (40 ml.). When potassium cyanide (1 g.) was added followed by water (10 ml.), the mixture immediately turned blue. After two hours it was filtered and the filtrate extracted with ether. The extract was treated in the usual way, and chromatography separated guaiazulene (5 mg.) and a trace of a hydrocarbon, λ max.625mμ, from a blue compound (benzene) which crystallised (petrol ether/ethanol) as purple needles, m.p.96-97.5°C.

Yield: 1.20 g., c.80%. (Found: C, 87.5; H, 7.3; N, 4.1. Phenyl guaiazulyl acetonitrile, $C_{23}H_{23}N$, requires C, 88.1; H, 7.4; N, 4.5%. A dinitrile, $C_{40}H_{40}N_{21}$, requires C, 87.5; H, 7.4; N, 5.1%).

(b) Under anhydrous condition.

The same quantity of the benzylidene-guaiazulenium chloride was suspended in dry benzene (50 ml.) and potassium cyanide (1 g.) added. The mixture was milled with glass beads for 6 hours and then left at room temperature overnight during which the solution became blue. It was filtered to remove unchanged benzylidene-guaiazulenium chloride, and taken to dryness. The residue, chromatographed in petrol ether solution, contained guaiazulene (92 mg.) and blue fractions (petrol ether(9)/benzene(1)) and (petrol ether(1)/benzene(1)). The former crystallised as a blue solid (petrol ether/ethanol), m.p. 156-157°C. Yield: 260 mg. (Found: C, 91.5; H, 8.8. $C_6H_5CH_2+2\underline{Gu}^{3\cdot4}+\underline{Gu}^{3}$, $C_{52}H_{56}$, requires C, 91.8; H, 8.2%). The second blue fraction was the product obtained in the reaction under aqueous conditions.

Reaction of m-bromo-benzylidene-guaiazulenium chloride with potassium cyanide.

The same methods were applied to this substituted benzylidene-guaiazulenium chloride. Under aqueous conditions,

the salt from 1 g. guaiazulene yielded guaiazulene (17 mg.), a blue fraction (petrol ether(2)/benzene(1)) which crystallised (petrol ether/ethanol) as a blue solid, mp. variable with rate of heating. Yield: 20 mg. (Found: C, 82.4; H, 7.6; Br, 10.3. $Br{\cdot}C_6H_4CH_2 + 2\underline{Gu}^{3\cdot4} + \underline{Gu}^3$, $C_{52}H_{55}Br$, requires C, 82.2; H, 7.3; Br, 10.5%), and a second blue compound (benzene) which crystallised (petrol ether/ethanol) as blue/green plates, m.p. variable. Yield: 510 mg. (Found: C, 77.0; H, 6.3; N, 4.4; Br, 12.5. $Br{\cdot}C_6H_4{\cdot}CH + \underline{Gu}^{3\cdot4} + \underline{Gu}^3 + CH + (CN)_2$, $C_{40}H_{39}N_2Br$, requires C, 76.5; H, 6.3; N, 4.5; Br, 12.7%). Using anhydrous conditions, the products were guaiazulene (53 mg.), the same hydrocarbon (83 mg.) (Found: C, 82.8; H, 7.7; Br, 9.9%), and the dinitrile (210 mg.).

Hydrolysis of phenyl guaiazulyl acetonitrile.

Phenyl guaiazulyl acetonitrile (200 mg.) was dissolved in ethanol (10 ml.), concentrated hydrochloric acid (2 ml.) was added and the solution boiled under reflux for 30 minutes. The solution changed to a brownish green colour. It was extracted with ether and the extract prepared for chromatography in the normal manner. The products were unchanged phenyl guaiazulyl acetonitrile (105 mg.) and yellow/green decomposition products.

In another experiment, phenyl guaiazulyl acetonitrile (1.49 g.) was dissolved in ethanol (100 ml.) and a 4% ethanolic

solution of sodium hydroxide (50 ml.) added. The solution immediately became green, red in transmitted light. After 1 hour, the solution was diluted with water and extracted with ether. The extract was treated in the normal way. Chromatography separated unchanged phenyl guaiazulyl acetonitrile (935 mg.) from an orange band (benzene(1)/ether(1)) which gave a green solution, red in transmitted light. Dark purple crystals were obtained (petrol ether/ethanol) m.p. 120-122°C. Mixed m.p. with benzoyl guaiazulene, 119-122°C. Yield: 230 mg. (Found: C, 87.5; H, 7.4. Benzoyl guaiazulene, $C_{22}H_{22}O$, requires C, 87.5; H, 7.3%).

Using the same method for alkaline hydrolysis of the dinitrile from the reaction of m-bromo-benzylidene-guaiazulenium chloride with potassium cyanide, the products were unchanged dinitrile and a brown compound, orange on alumina, which crystallised (methanol) as brown needles, m.p. 81-82.5°C. Yield: 80 mg. from 100 mg. starting material, 80%. (Found: C, 75.4; H, 7.0; Br, 13.3. The corresponding diketone, $BrC_6H_4 + \underline{Gu}^{3\cdot4} + \underline{Gu}^{3} + (CO)_2$, $C_{38}H_{37}O_2Br$, requires C, 75.3, H, 6.1; Br, 13.2%).

The nitrogen containing compound from the action of potassium cyanide on benzylidene-guaiazulenium chloride was examined by X-ray methods. The volume of the unit cell was found to be $913A^3$ and the density of the material to be 1.07 g./cc.

The molecular weight was hence calculated to be 588/n, where n is the number of molecules per unit cell. The most probable value for this is 2, therefore the molecular weight may be 294 (or less probably 588). The monoclinic crystals of the ketone to which it hydrolyses were found to have cell volume 1697.3A^3 and density 1.19 g./cc. The mass in the unit cell was calculated from this to be 1216. Since the nature of the crystal suggests that there are four molecules per unit cell, the molecular weight is most probably 304. This agrees with the value for benzoyl guaiazulene which is 302. The molecular weight of the nitrile from which this ketone was derived will therefore be 313, that of phenyl guaiazulyl acetonitrile.

Reaction of o-methoxy-benzylidene-guaiazulenium chloride with potassium cyanide.

The o-methoxy-benzylidene-guaiazulenium chloride prepared from 400 mg. guaiazulene was added to an aqueous solution of potassium cyanide (1 g.) which turned blue immediately. It was extracted with ether, and the extract washed with water, dried and concentrated to 25 ml. A mixture of ethanol (25 ml.) and 10% aqueous sodium hydroxide (25 ml.) was added but there was no colour change. Air was bubbled through the solution and after 30 minutes there was a trace of green in the aqueous layer. The passage of air was then stopped and the flask stoppered.

The next day the solution was extracted with ether and the extract prepared for chromatography. The first fraction was yellow, and the second (petrol ether (1)/benzene(1)) blue. It was taken to dryness and a green impurity extracted from it with petrol ether. The remaining bright blue solid was recrystallised from ethyl acetate, m.p. c.160°C., variable with rate of heating. Yield: 220 mg. (Found: C, 84.8; H, 7.4; N, 3.8. o-Methoxy-phenyl-3-guaiazulyl-acetonitrile, $C_{24}H_{25}NO$, requires C, 83.9; H, 7.4; N, 4.1%). There was also an orange band (ether) which gave a blue solution, red in transmitted light. It could not be crystallised even after extraction into concentrated hydrochloric acid and regeneration by dilution.

Reaction of p-nitro-benzylidene-guaiazulenium chloride with potassium cyanide.

The p-nitro-benzylidene-guaiazulenium chloride prepared from 500 mg. guaiazulene was added to an aqueous solution of potassium cyanide (1 g.). The solution which became green was extracted with ether. It was treated in the normal way, but it was necessary to use benzene to dissolve the material for the chromatogram since it was insoluble in petrol ether. The products were a small quantity of guaiazulene and a blue/green fraction (petrol ether(1)/benzene(1)) which yielded 70 mg. of a blue solid, m.p. 205°C. (Found: C, 83.1; H, 7.5; N, 3.2.

$(NO_2C_6H_5CH)_2$ + $\underline{Gu}^{3\cdot4}$ + $2\underline{Gu}^{3}$, $C_{59}H_{62}N_2O_4$, requires C, 82.3; H, 7.0; N, 3.3%).

There was also a yellow/green fraction (benzene) and a purple band which gave a green solution (ether(9)/ethanol(1)). The latter was purified by extraction into 75% hydrochloric acid and regenerated by dilution but it did not crystallise. Distillation at 0.5 mm. pressure caused it to decompose.

Reaction of benzylidene-guaiazulenium chloride with p-chloro-aniline.

p-Chloro-aniline (1.6 g.) was added to a solution in dry benzene (50 ml.) of benzylidene-guaiazulenium chloride prepared from 1 g. guaiazulene. The colour changed to blue within a few minutes and after half an hour the solution was filtered to remove unchanged material and p-chloro-aniline hydrochloride. The benzene solution was taken to dryness by distillation under reduced pressure and the residue chromatographed in petrol ether solution. The products were a small quantity of guaiazulene and a second blue fraction (petrol ether) which was rechromatographed and then crystallised as light blue needles (petrol ether/ethanol), m.p.125-126°C. Yield: 710 mg. (Found: C, 91.9; H, 8.3; N, nil; Cl, nil. PhCH + $3\underline{Gu}$ + C_2H_4, $C_{34}H_{61}$, requires C, 91.4; H, 8.6%).

Reaction of benzylidene-guaiazulenium chloride with aniline.

Aniline (0.5 g.) was mixed with dry benzene (40 ml.) and the benzylidene-guaiazulenium chloride prepared from 1 g. guaiazulene added. The solution turned blue immediately, but a quantity of red material remained unreacted even after warming the mixture with a further quantity of aniline. The solution was then kept at room temperature for 30 minutes, filtered, extracted with ether, and the extract prepared for chromatography. The products were a small quantity of guaiazulene, blue/green fractions (petrol ether(9)/benzene(1)) and (benzene(1)/ether(1)) and a trace of blue material (ether). The first blue/green fraction crystallised (petrol ether/ethanol) as a blue solid which decomposed after some time to a brown colour, m.p. 125-127°C. Yield: 290 mg. (Found: C, 90.8; H, 8.5; N, 0.6%. $C_6H_5CH + 2\underline{Gu} + C_2H_4$, $C_{54}H_{67}$ requires C, 91.4; H, 8.6%). The other decomposed during distillation of the solvent at atmospheric pressure to a green material which did not crystallise.

Reaction of m-bromo-benzylidene-guaiazulenium chloride with aniline.

Aniline (0.5 g.) was dissolved in dry benzene (40 ml.) and the m-bromo-benzylidene-guaiazulenium chloride prepared from 1 g. guaiazulene added. The colour of the benzene

solution gradually changed to blue. A solution of aniline in benzene was then added until almost all of the red chloride had reacted. The solid was filtered off after 15 minutes and the blue solution taken to dryness by distillation under reduced pressure. The residue, chromatographed in petrol ether solution, contained guaiazulene (106 mg.) and a blue substance (petrol ether (2)/benzene(1)). The latter crystallised as bright blue needles (petrol ether/ethanol), m.p. c.210°C. (variable with rate of heating). (Found: C, 83.7; H, 7.4; N, nil; Br, 9.4%. BrC_6H_4CH + 3Gu + C_2H_4, $C_{54}H_{60}Br$, requires C, 82.1; H, 7.6; Br, 10.1%).

Action of sodamide on guaiazulene.

In an attempt to substitute guaiazulene in the seven-membered ring, guaiazulene was added to a solution of a large excess of sodamide in liquid ammonia. The temperature of the mixture was allowed to rise to that of the room, and then dimethylaniline was added, and the solution heated to boiling. It was then poured into water forming a yellow aqueous phase which turned orange on acidification. Nothing could be isolated from it, but the dimethylaniline phase, after normal treatment and chromatography, yielded a large quantity of unreacted guaiazulene and a green dimer, m.p. 136-143°C. T.N.B. complex, m.p. 188°C. Yield: 5.8 mg., 1.4%.

In a second reaction, the guaiazulene (210 mg.) was added in benzene (40 ml.) to the sodamide in liquid ammonia (50 ml.). After the solution rose to room temperature, it was warmed to about 60°C. and then water and ether added. The phases were then separated. The aqueous one was again yellow, but the ether/benzene phase contained guaiazulene (4.5 mg.) and a blue solid (petrol ether(3)/benzene(1)), m.p. 151-152°C. Yield: 8 mg., 3.8%. A micro Rast determination showed it to be another dimer of guaiazulene. There were also small quantities of green and greenish/yellow products eluted by benzene and by ether. When ethyl chloroformate was added to the reaction mixture, the same products were obtained. The two dimers both had the same spectrum as guaiazulene. The formation of a blue dimer by the action of sodamide is a confirmation of previous work by D.H. Reid. He has also reported the formation of a green dimer, m.p. 142-143°C., by the action of stannic chloride on guaiazulene.